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Workforce Team

Editors-in-chief

Yasmine Yehia Mostafa	Manager of Clinical Pharmacy Unit - Drug Utilization and Pharmacy Practice General Administration – Egyptian Drug Authority
Lamis Diaa Saeed	Manager of Medication Consulting Unit - Drug Utilization and Pharmacy Practice General Administration – Egyptian Drug Authority
Abdulrahman Mohamed Amin	Manager of NO HARMe Unit - Drug Utilization and Pharmacy Practice General Administration – Egyptian Drug Authority
Hebatullah M. AbdulAziz	Manager of Clinical Pharmacy Practice Administration and Drug Information Administration - Drug Utilization and Pharmacy Practice General Administration – Egyptian Drug Authority
Under Supervision of	
Dr. Shereen Mohamed AbdelGawad	Head of the Central Administration of Pharmaceutical Care - Egyptian Drug Authority - Head of Pharmacy Practice Guides and National Drug Lists Committee
Dr. Abeer Elbehairy	General Manager of Drug Utilization and Pharmacy Practice Administration – Egyptian Drug Authority

Editorial Board

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Prof. Mohamed Farag Alyamany	Professor of Pharmacology and Toxicology Faculty of Pharmacy - Cairo University
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Dr. Mariam Soliman El-Debeiky	Manager of the Medical Technology Reassessment Department at the Unified Procurement Authority (UPA)
Prof. Nirmeen Ahmed Sabry	Professor of Clinical Pharmacy – Faculty of Pharmacy - Cairo University – Medication Management Consultant
Dr. Sherif Kamel Eldeen	Chairman Consultant of Egyptian Healthcare Authority for Pharmacy Affairs

Special Thanks to

Kholuod Ahmed Alnaggar	Manager of Drug Awareness Administration - Drug Utilization and Pharmacy Practice General Administration – Egyptian Drug Authority
Mohamed Elsayed Eldesoky	Former Member of Drug Utilization and Pharmacy Practice General Administration – Egyptian Drug Authority
Monica Magdy	Former Member of Drug Utilization and Pharmacy Practice General Administration – Egyptian Drug Authority

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Abbreviations List

Table (1) Abbreviations List

A1C	Glycated hemoglobin
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ACR	Albumin to Creatinine Ratio
ADA	American Diabetes Association
ADL	Activities of Daily Living
AE	Adverse Effect
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
ARBs	Angiotensin Receptor Blocker
ASCVD	Atherosclerotic Cardiovascular Disease
BGM	Blood Glucose Monitoring
BG	Blood Glucose
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CAN	Cardiac Autonomic Neuropathy
CCB	Calcium Channel Blocker
CGM	Continuous Glucose Monitoring
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
DASH	Dietary Approach to Stop Hypertension
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DKD	Diabetic Kidney Disease
DM	Diabetes Mellitus
DN	Diabetic Neuropathy
DPN	Diabetic Peripheral Neuropathy
DPP-4i	Dipeptidyl Peptidase-4 Inhibitor
DSMES	Diabetes Self-Management Education and Support
DSPN	Distal Symmetric Polyneuropathy
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FDA	Food And Drug Administration (in the United States)
FITT	Frequency, Intensity, Time, Type
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
GH	Growth Hormone
GMI	Glucose Management Indicator
GLP-1RAs	Glucagon-like Peptide -1 Receptor Agonists
HDL	High-Density Lipoprotein
HF	Heart Failure

HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HHS	Hyperosmolar Hyperglycemia State
HIV	Human Immunodeficiency Virus
HRV	Heart Rate Variability
ICR	Insulin to Carbohydrate Ratio
IFG	Impaired Fasting Glucose
IGF-1	Insulin-Like Growth Factor-1
IGT	Impaired Glucose Tolerance
IM	Intramuscular
ISF	Insulin Sensitivity Factor
IT	Information Technology
IV	Intravenous
IWGDF	International Working Group on The Diabetic Foot
KDIGO	Kidney Disease Improving Global Outcomes
LAA	Long-Acting Insulin Analogs
LC	Low Carbohydrate
LDL	Low-Density Lipoprotein
LF	Low-Fat
LOPS	Loss of Protective Sensation
LTC	Long-term Care
MDI	Multiple Daily Injections
MI	Myocardial Infarction
MNT	Medical Nutrition Therapy
NAFLD	Nonalcoholic Fatty Liver Disease
NGSP	National Glycohemoglobin Standardization Program
NPH	Neutral Protamine Hagedorn
NPO	Nothing Per Oral
OGTT	Oral Glucose Tolerance Test
OSA	Obstructive Sleep Apnea
PAD	Peripheral Artery Disease
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PPG	Post-Prandial Plasma Glucose
PO	Per Oral
R	Regular Insulin (Short-Acting)
RAA	Rapid-Acting Insulin Analogs
RAAS	Renin Angiotensin-Aldosterone System
RPG	Random Plasma Glucose
ROI	Return On Investment
SC	Subcutaneous
SDOH	Social Determinants Of Health
SGLT2i	Sodium-Glucose Cotransporter 2 Inhibitor
SIRS	Systemic Inflammatory Response Syndrome
SU	Sulfonylurea
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TDD	Total Daily Insulin Dose

TIR	Time In Range
TZD	Thiazolidinedione
UACR	Urine-Albumin Creatinine Ratio
URAA	Ultra-rapid-acting Insulin Analogs
VLC	Very Low Carbohydrate
VLF	Very Low Fat
WHO	World Health Organization

Level of Evidence

Table (2) Level of Evidence of American Diabetes Association "ADA" adapted from *(ElSayed et al., 2023a)*

Level of evidence	Description
A	▪ Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including: - Evidence from a well-conducted multicenter trial. - Evidence from a meta-analysis that incorporated quality ratings in the analysis. ▪ Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: - Evidence from a well-conducted trial at one or more institutions. - Evidence from a meta-analysis that incorporated quality ratings in the analysis.
B	▪ Supportive evidence from well-conducted cohort studies - Evidence from a well-conducted prospective cohort study or registry. - Evidence from a well-conducted meta-analysis of cohort studies. ▪ Supportive evidence from a well-conducted case-control study
C	▪ Supportive evidence from poorly controlled or uncontrolled studies - Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results. - Evidence from observational studies with high potential for bias (such as case series with a comparison with historical controls). - Evidence from case series or case reports. ▪ Conflicting evidence with the weight of evidence supporting the recommendation
E	▪ Expert consensus or clinical experience

Table (3) Level of Evidence of Kidney Disease Improving Global Outcomes "KDIGO" adapted from *(KDIGO,2022)*

Grade	Quality of evidence
A	▪ High
B	▪ Moderate
C	▪ Low
D	▪ Very low

Table (4) Level of Evidence of International Working Group on The Diabetic Foot "IWGDF" adapted from (*Senneville et al., 2023)*

Strength of recommendation	Description	Quality of evidence	Description
Strong	▪ Guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects or that the undesirable effects of an intervention outweigh its desirable effects. ▪ A strong recommendation implies that most or all individuals will be best served by the recommended course of action.	High	▪ We are very confident that the true effect lies close to that of the estimate of the effect.
Conditional	▪ The desirable effects probably outweigh the undesirable effects or undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. ▪ A weak recommendation implies that not all individuals will be best served by the recommended course of action. There is a need to consider more carefully than usual the individual patient's circumstances, preferences, and values.	Moderate	▪ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
		Low	▪ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

		Very low	▪ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Introduction and Methodology

Introduction

Diabetes Mellitus is one of the most prevalent diseases in Egypt. According to World Bank statistics in 2021, 20.9 % of the Egyptian population suffers from diabetes mellitus ***(World Bank, 2021).*** This makes healthcare providers deal with diabetic patients in a significant way. This has drawn attention to the need for a comprehensive guide to good pharmacy practice when dealing with diabetic patients. In this guide, you will find clear information about diabetes prevention, screening and referral, glycemic control and target levels, and diagnostic criteria for diabetes. Additionally, it includes sections on treatment approaches for diabetes types 1 and 2, along with the various management options available - including insulins and oral anti-diabetics. The role of non-pharmacological approaches in treating diabetes and its associated complications is also discussed in the guide so that the patient's quality of life can be improved dramatically.

Pharmacists should likewise be well-informed about the latest diabetes treatments and how to counsel patients on lifestyle changes. Pharmacists also need to be knowledgeable and able to evaluate the efficacy of prescribed treatments in their patients. They should also be able to advise monitoring diabetes and anti-diabetic drugs.

In preparing this guide, we have worked hard to raise the standard of service provided to patients and to assist pharmacists in performing their jobs more effectively. Thus, we achieve our goals of improving the healthcare system.

In this regard, the General Administration of Drug Utilization and Pharmacy Practice plays its assigned role in upgrading pharmacy practices and taking successive steps towards unifying them. It complements the Egyptian Drug Authority’s efforts in issuing guides for the pharmacist's role as one of the pillars of the healthcare system.

Aim and Scope

This guide is developed as a comprehensive manual for pharmacists who aim to deliver the best patient care, hence, it is based on the most accurate and reliable information available. However, it is important to emphasize that any clinical procedure or treatment plan must be determined by the responsible healthcare provider in accordance to clinical evidence. By using this guide as a valuable resource, pharmacists can make informed recommendations and provide optimal pharmacy practice. This could be done by complying with international guidelines, promoting the rational use of medications, in addition to providing sufficient drug awareness and patient education according to the specific needs.

To ensure that every patient receives the highest quality of care, this guide focuses on pharmacist in both the community and hospital pharmacy sectors. By upgrading their services, pharmacists can better meet the diverse and ever-evolving needs of their patients.

By implementing the recommendations outlined in this guide, we can improve the overall health outcomes of our patients. So let us strive towards excellence in pharmacy practice by delivering outstanding care to every patient we serve.

Target population: The guide aims to provide information about diabetes and its associated complications. It covers adult patients with diabetes, including those with type 1 and type 2 diabetes, and those at high risk of developing diabetes. While gestational diabetes is briefly reviewed, the guide does not discuss diabetes in pediatrics or adolescents.

Target end users include clinical, and hospital pharmacists, working in inpatient and outpatient settings, in addition to community pharmacists.

Target settings include primary, secondary, and tertiary healthcare facilities and community pharmacies. Making it possible to deliver effective services that ensure the health and well-being of the population at a large scale.

Methodology

Work teams were formed by the General Administration of Drug Utilization and Pharmacy Practice members to draft the guide. They referred to scientific references and evidence-based guidelines and discussed the latest research published in accredited resources and peer-reviewed journals. As stated in the EDA chairman’s decree number (185) / 2023, for the establishment of (Pharmacy Practice Guides and National Drug Lists Committee), the guide was discussed and reviewed thoroughly by the committee members. The work team amended the draft. The required steps to approve, publish, and circulate the guide have been completed.

Conflict of Interest

Editors-in-chief, editorial board members, and staff avoided any conflicts or appearance of conflicts between their interests and those of the guide's committee when preparing, reviewing, and modifying its contents. All parties confirmed they do not have any personal or business interest in or potential for personal gain from any of the organizations or projects linked to this guide, nor do any of their relatives or businesses. Furthermore, they confirmed that they know of no other actual, potential, or apparent conflict of interest.

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Outpatient Settings

Pharmacists' Roles in Diabetic Patient Care

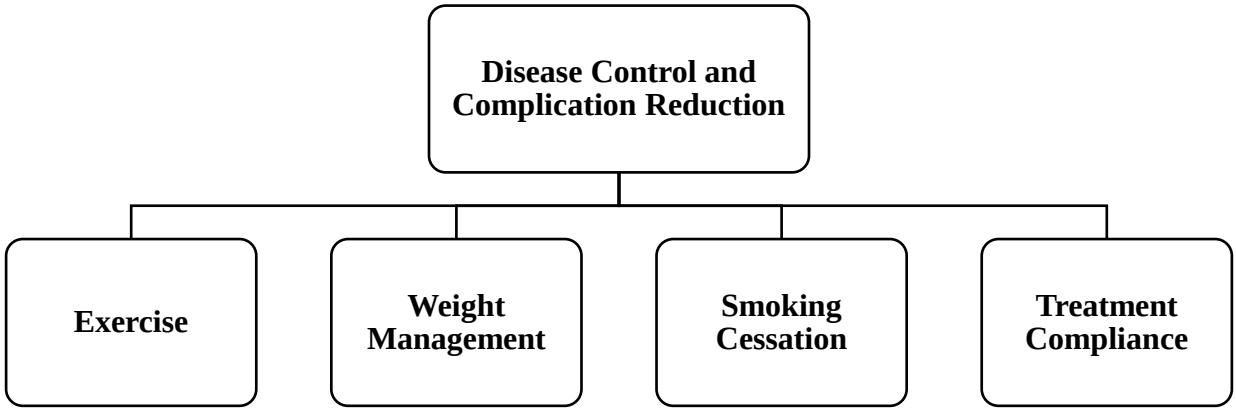
Outpatient Settings: Pharmacists' Roles in Diabetic Patient Care

- Ambulatory care facilities play an important role in chronic disease management such as diabetes by providing outpatient services and assisting patients with self-management. Effective chronic illness management in ambulatory care prevents complications, decreases hospitalizations, and improves patients' overall health ***(Hobbick, 2024).***
- Diabetes management necessitates a multifaceted approach that includes lifestyle-related factors, medication-related aspects, self-monitoring, and continual follow-up. This strategy enhances the need for specialized services and a multidisciplinary collaborative care paradigm in diabetes management to improve clinical results, lower the risk of complications, ensure medication and patient safety, and enhance medication adherence. Many non-communicable disorders, such as diabetes, hypertension, asthma, and arthritis, have been found to benefit from pharmacist-led interventions. Pharmacist-led interventions have been found to enhance clinical outcomes in diabetic patients ***(Abdulrhim et al., 2019).***
- Outpatient settings such as primary health care (PHC) centers, hospital-based outpatient clinic, and community pharmacies ***(Dodd et al., 2022).***
  - **Primary health care (PHC) centers:** Everyone, everywhere has the right to reach the best possible level of health. This is the core principle of PHC ***(WHO, 2019).*** A PHC center serves as the first point of contact for the management of several diseases, including diabetes ***(Lall et al., 2020).***
  - **Community pharmacies:** The community pharmacy is increasingly recognized as the initial point of contact for people seeking assistance with chronic disease management; it is local and easily accessible. The average diabetic patients visit a community pharmacy 3-8 times more frequently than other patients. Therefore, community pharmacists can play a critical role in managing diabetes and its complications ***(Ali et al., 2012).***
- **<u>Pharmacists' roles in diabetic patient care in outpatient settings</u>**
  - Providing, securing, and storing medications properly ***(Management Science for Health, 2012; Meena et al., 2022).***
  - **Monitoring** the inventory regularly and checking expiration dates to ensure the safety and efficacy of medications ***(Malasari & Sudrajat, 2024; Management Science for Health, 2012).***
  - **Medication review** before dispensing to detect any drug-related problems and communicate with physicians to resolve them before dispensing such as actual and potential drug-drug, drug-disease, drug-nutrient, and drug-laboratory test interactions; drug duplication; and drug allergy ***(Al Assaf et al., 2022; Hughes et al., 2017).***
  - **Dispensing** medications properly with clear and accurate labeling ***(The Pharmacy Guild of Australia, 2016).***
  - **Reporting** medication errors and adverse drug reactions and sent to the relevant authorities ***(VA Center for Medication Safety, 2006)***. (Refer to NO HARMe and EPV links on the EDA official website, QR codes on page 149)
  - **Patient education**: Education focuses on raising diabetic patients' knowledge about their disease, its complications, and how to prevent or delay their occurrence. Education should include the following information ***(Hughes et al., 2017; Mehuys et al., 2010):***

1) Educating Patients about Diabetes as A Disease

- **Diabetes is a disease** in which the blood sugar level is high and is caused by a defect in the hormone insulin secreted by the pancreas ***(ADA, 2009).***
- This defect includes either not secreting any insulin "as happens in the first type of diabetes", the amount of insulin is insufficient, or the insulin does not work properly "as happens in the second type of diabetes" ***(ADA, 2009; Gary-JayBourley, 2024).***
- **There are generally two types of diabetes:**
  - **Type 1:** This type cannot be prevented and begins at an early age. However, it can be developed at any age ***(Gary-JayBourley, 2024).***
  - **Type 2:** It begins gradually and usually late in life, and because the symptoms may not be clear, years may pass before discovering. This type can be prevented and delayed ***(Gary-JayBourley, 2024; NIDDK, 2016).***
- **Rarely, if the cause of diabetes is excessive obesity, which affects the proper functioning of insulin (insulin resistance), then when obesity is treated, diabetes is cured** ***(ElSayed et al., 2023b).***

2) Educating Patients about Diabetes Control



Excercise	**Before exercise** Diabetic patients should be assessed before, during, and after beginning physical activity by a specialized healthcare provider to identify any cardiovascular risk factors and disorders that may limit certain types of exercise ***(Raveendran, 2018; Riddell et al., 2024).***
	Exercise regimen The most suitable exercise regimen is ≥ 150 minutes per week of moderate-intensity aerobic exercise, such as brisk walking "spread the 150 minutes over the week as an every other day regimen as exercise-induced improvement in insulin sensitivity lasts between 24 and 72 hours" ***(Blum et al., 2021; ElSayed et al., 2023c; Delahanty et al., 2023; Raveendran, 2018; Riddell et al., 2024).***
	After exercise Educate the patients about ***exercise-induced hypoglycemia***, which may occur during, shortly after, or many hours after exercise, and highlight the importance of frequent glucose monitoring to assess their glycemic response to exercise and, if necessary, refer to the physician to adjust insulin/secretagogue agent doses and carbohydrate regimens to avoid hypoglycemia ***(Cryer et al., 2024; Delahanty et al., 2023; Delahanty et al., 2024).***
	To reduce the early post-exercise hypoglycemia, the patient should spread brief episodes of intense exercise, add carbohydrate ingestion (e.g., 1 g/kg/h), and reduce insulin doses according to physician assessment ***(Cryer et al., 2024).***
Weight Management	Educate the patient about the importance of physical activity and healthy diet in the management of their weights ***(Delahanty et al., 2024; Raveendran, 2018).***
	This is particularly important as modest weight loss improves glycemia and reduces the need for glucose-lowering medications in people with type 2 diabetes mellitus (T2DM) who are overweight or obese ***(ElSayed et al., 2023b).***
	Furthermore, larger weight loss significantly reduces glycated hemoglobin (A1C) and Fasting Plasma Glucose (FPG) and has been shown to promote sustained T2DM remission ***(ElSayed et al., 2023b).***
	Medication use, or bariatric surgery may also be used for weight management according to the physician assessment ***(Delahanty et al., 2024; ElSayed et al., 2023b; Raveendran, 2018).***

Smoking Cessation	Smoking can hasten the progression of the disease and raise the risk of complications in people with type 1 or type 2 diabetes such as heart and kidney complications, peripheral artery disease (PAD), diabetic foot infections or ulcers, potential amputation of the toes or feet, retinopathy and peripheral neuropathies ***(Blum et al., 2021; ElSayed et al., 2023d; NIDDK, 2021).***
	Smoking also affects insulin function. As insulin is less effective in the presence of nicotine. When exposed to high levels of nicotine, the body requires more insulin to control blood glucose levels ***(Blum et al., 2021).***
Treatment Compliance	Treatment compliance is critical to control blood glucose, blood pressure, lipid profile, and cardiovascular diseases ***(Blum et al., 2021; ElSayed et al., 2023d; Mutlaq, 2020).***

3) Educate Patients about Diabetes Complications

- Educate the patients about the importance of compliance with regular monitoring and examinations ordered by physicians to control the disease, and avoid any delayed diabetic complications such as diabetic nephropathy, retinopathy, neuropathy, and cardiovascular complications ***(EmmaW, 2024).*** For further details about regular checkups for diabetic patients refer to the *Monitoring Patients with Diabetes Mellitus* chapter.
- Educate the patients about the importance of the healthcare provider consultation if there's a fever or suspected infection ***(Kitabchi et al., 2009).***

Hypoglycemia *Educate your patient about*	**Risk factors contributing to hypoglycemia** These factors include excessive physical activity, fasting, inappropriate doses, wrong insulin type, and others ***(Cryer et al., 2024).***
	Symptoms of hypoglycemia Such as tremor, palpitations, anxiety/arousal and sweating, hunger, paresthesias, dizziness, weakness, drowsiness, delirium, confusion, and, at lower plasma glucose concentrations, seizure, and coma ***(Cryer et al., 2024).***
	Hypoglycemia should be treated promptly as episodes are reversible after raising the glucose level. If left untreated, profound, prolonged hypoglycemia can cause brain death ***(Cryer et al., 2024).***
	The patient's medications should be adjusted based on glucose patterns, and the target glucose and A1C levels should be reviewed if needed. Patients should be referred to their phyicians to adjust their medications, meals, and exercise based on their patterns and caregivers should be taught to recognize severe hypoglycemia ***(Cryer et al., 2024).***
	Patients with severe hypoglycemia should be immediately transferred to the hospital ***(ElSayed et al., 2023e).***

Hyperglycemia

Educate your patient about

Risk factors contributing to hyperglycemia

These factors include infection, insulin omission, inadequate dose medication, some medications as corticosteroids, and others ***(Kitabchi et al., 2009).***

Symptoms of hyperglycemia

Such as polyuria, polydipsia, weakness, and changes in mental status, presence of fruity odor in the breath, signs of dehydration, (e.g., dry mucous membranes, poor skin turgor, tachycardia, hypotension, and increased capillary refill in severe dehydration), and unconsciousness "if it is left untreated" ***(Aldhaeefi et al., 2022).***

Sick days (days during acute illness) management

Educate the patients about the assessement and documentation of body temperature, measurement blood glucose, and the importance of adherence to diabetes medications ***(Kitabchi et al., 2009).***

The proper use of home glucose-ketone meters that may aid the patient in the early recognition and management of upcoming ketoacidosis ***(Kitabchi et al., 2009).***

Educate the patient to get an easily digestible liquid diet with carbohydrates and salt when nauseated to prevent diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) ***(Kitabchi et al., 2009).***

Mouth Problems

Educate your patient about

Symptoms of mouth problems

Symptoms that should be checked are red, swollen, bleeding, pulling away from teeth, or sores on the gums (gingivitis); loose teeth due to untreated periodontitis (gum and bone infection that hold the teeth in place); increased space between teeth; a dry mouth that can lead to soreness, ulcers, infections, and tooth decay; painful, white spots in the mouth due to a fungal infection (thrush); persistent bad breath, even after having brushed teeth; pain, and chewing difficulties ***(ADA, 2023; CDC, 2023; CDC, 2024; NIDCR, 2023; NIDDK, 2022).***

Dental care should be performed daily, and regular visits to the dentist should be made every six months. Brush teeth with a soft-bristled toothbrush at least twice a day with fluoride toothpaste and floss at least once a day ***(ADA, 2023; CDC, 2023; CDC, 2024; NIDCR, 2023; NIDDK, 2022).***

The patient should also be advised to limit sugary foods and beverages and consume healthy foods and beverages ***(CDC, 2023).***

Diabetic Foot

Educate your patient about

Inspect and examine both feet daily {the entire surface, paying particular attention to areas between the toes} ***(Schaper et al., 2023).***

Cut toenails appropriately {cut toenails straight across} ***(Schaper et al., 2023).***

Avoid walking barefoot, in socks without footwear, or in thin-soled slippers, whether indoors or outdoors, to protect the feet ***(Schaper et al., 2023).***

Avoid wearing shoes that are too tight, and have rough edges or uneven seams. Wear appropriate footwear, the inside of the shoe should not be too tight or too loose; it should be 1-2 cm longer than the foot. The height should enable space for all the toes, and the internal width should be equivalent to the width of the foot at the metatarsal phalangeal joints {or the widest part of the foot} ***(Schaper et al., 2023).***

Instruct the patient to never wear the same shoe that has caused an ulcer ***(Schaper et al., 2023).***

Advise the patient to wash feet every day (water temperature should never exceed 37°C), and dry them properly, paying close attention to areas between the toes ***(Schaper et al., 2023).***

Advise against using chemical agents or plasters to remove corns and calluses; refer to the appropriate healthcare professional for these issues ***(Schaper et al., 2023).***

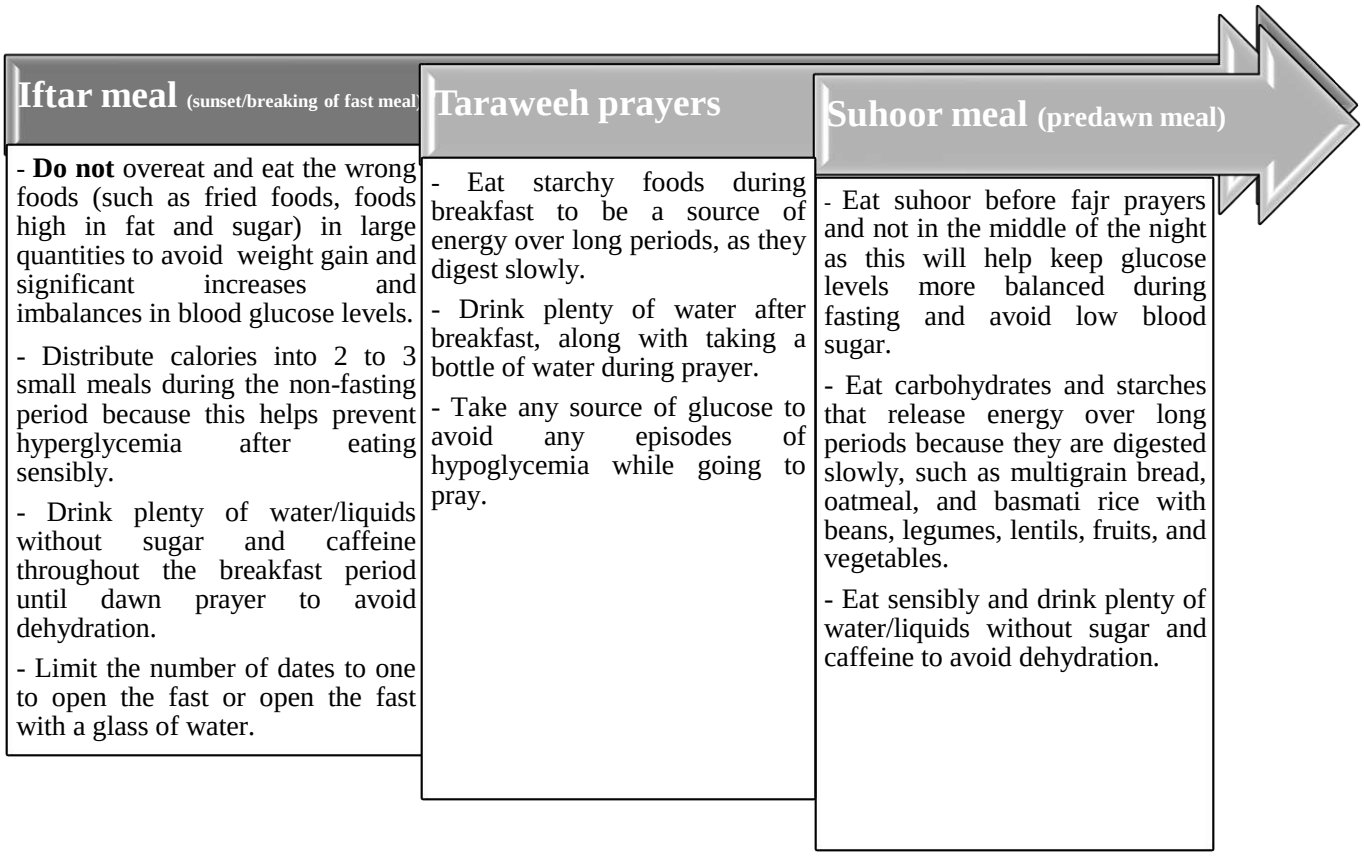
Use emollients to lubricate dry skin, but avoid using them between the toes ***(Schaper et al., 2023).***

Advise self-monitor foot skin temperatures once daily to detect early signs of inflammation and help prevent a foot ulcer. If the temperature increases and there is a difference between similar regions in the two feet on two consecutive days, the patient should reduce ambulatory activity and contact his healthcare team ***(Schaper et al., 2023).***

Immediately contact healthcare professionals if the foot temperature is observable increased, or if there is a new blister, cut, scratch, or ulcer ***(Schaper et al., 2023).***

4) Educate Patients about Fasting and Diabetes

- Educate the patient about fasting in Ramadan as fasting is sometimes safe, despite having diabetes, but the patient must talk to the medical team before starting fasting, and based on the evaluation of the patient's condition, the medical team will provide the best advice to the patient as follows ***(Al-Arouj et al., 2010; BridgetChapple, 2024; Diabetes Australia, 2022; Diabetes UK, 2014):***



General instructions for diabetic patients for fasting	Carry a source of glucose in your pocket to avoid any comas in case of low blood sugar at any time, while monitoring the appearance of signs of low blood sugar throughout the fasting period ***(BridgetChapple, 2024; Diabetes UK, 2014).***
	Test Test sugar frequently, especially for patients who take insulin, and especially when feel any fatigue during fasting. This procedure does not break the fasting ***(Al-Arouj et al., 2010; Diabetes Australia, 2022; Diabetes UK, 2014).*** .
	Avoid excessive physical activity, especially during the fasting period, to avoid hypoglycemia, and practice any sport preferable two hours after sunset meal ***(Al-Arouj et al., 2010).***
	Do not stop taking insulin or any medications that treat diabetes or hypertension, but consult a doctor to change the doses and times ***(Al-Arouj et al., 2010; Diabetes UK, 2014).***
	Avoid fasting on "sick days" and end fasting immediately if ***(Al-Arouj et al., 2010; Diabetes UK, 2014):*** - Blood sugar level is <(60 mg/dL), blood sugar level is >(300 mg/dL). - Blood sugar level is (70 mg/dL) at the beginning of fasting after already taking insulin or sulfonylurea drugs, or meglitinide or in case of dehydration, feeling tired, confused, or faint.

Illustration (1) Patient Education Items

- **Medication Counselling:** The patients need to understand their drugs and modifications to their lifestyle for better blood glucose control. This is done by several methods such as face-to-face counseling or delivering printed educational material ***(Al Assaf et al., 2022; Hughes et al., 2017; Venkatesan et al., 2012).*** For good medication counseling, the pharmacist should:
  - Counsel the patient about the benefits and side effects of therapy with the understanding that therapy relieves symptoms but does not cure the disease ***(Venkatesan et al., 2012).***
  - Counsel on non-pharmacological measures such as a healthy diet, regular exercise, and smoking cessation ***(Al Assaf et al., 2022; Hughes et al., 2017; Mehuys et al., 2010; Venkatesan et al., 2012).***
  - Counsel the patient about medication side effects such as hypoglycemia, especially in case of taking insulin or insulin secretagogues ***(Al Assaf et al., 2022). "For details, refer to the Egyptian Drug Formulary – Endocrine Drugs Chapter" on the EDA website.***
  - Counsel the patient to take a missed dose as soon as possible, unless it is almost time to take the following dose. Avoid doubling the doses with close monitoring of blood glucose ***(Venkatesan et al., 2012).***
  - Counsel on regular self-monitoring of blood glucose especially in patients with type 1 diabetes and type 2 diabetes on insulin ***(Al Assaf et al., 2022; Cryer et al., 2024; Hughes et al., 2017).*** Patients may perform blood glucose monitoring (BGM) before and 2 to 3 hours after each meal, at bedtime, in the middle of the night, and before and after exercise ***(Cryer et al., 2024).***
  - Counsel on avoiding other medications, without physician approval ***(Venkatesan et al., 2012).***

- Counsel the patients about how to take their medication in the proper dosage, storage, actual and potential adverse drug events, proper technique, sites of injection, and proper time "timing about food" ***(Al Assaf et al., 2022; Mehuys et al., 2010)*** as follows:

Table (5) Administration of Oral Diabetic Medications

Oral Medications	
Medication	**Administration**
Biguanides	
Metformin	• ***Immediate release***: Administer with a meal (to decrease GIT upset) ***(Metformin 2024).*** • ***Extended-release:*** Swallow whole; do not crush, cut, or chew. Administer once-daily doses with an evening meal ***(Metformin 2024).***
Sulfonylureas (SU)	
Chlorpropamide	• Administer 30 minutes before a meal to improve absorption ***(Chlorpropamide 2024).***
Glibenclamide	• Administer with meals at the same time each day ***(Glibenclamide 2024).***
Glipizide	• ***Immediate release***: Administer 30 minutes before a meal (preferably before breakfast if once-daily dosing) to achieve the highest reduction in postprandial hyperglycemia ***(Glipizide 2024).*** • ***Extended-release***: Administer with breakfast or the first meal of the day; swallow tablets whole, do not chew, divide, or crush ***(Glipizide 2024).***
Glimepiride	• Administer once daily with breakfast or the first main meal of the day ***(Glimepiride 2024).***
Gliclazide	• Administer with meals (modified-release tablet should be administered with breakfast) ***(Gliclazide 2024).*** • May split the 60 mg modified-release tablets in half; however, the 30 mg modified-release tablets must be swallowed whole ***(Gliclazide 2024).*** • Modified-release tablets should not be crushed or chewed ***(Gliclazide 2024).***
Meglitinides	
Nateglinide, Repaglinide,	• Administer within 30 minutes before meals ***(Nateglinide 2024; Repaglinide 2024).***
Thiazolidinedione (TZD)	
Pioglitazone	• May be administered without regard to meals ***(Pioglitazone 2024).***
Dipeptidyl peptidase-4 inhibitors (DPP-4i)	
Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin,	Administer without regard to meals ***(Alogliptin 2024; Linagliptin 2024; Saxagliptin 2024; Sitagliptin 2024; Vildagliptin 2023).***
Sodium-glucose cotransporter 2 inhibitors (SGLT2i)	
Canagliflozin Dapagliflozin, Empagliflozin, Ertugliflozin	• Administer in the morning with or without food ***(Canagliflozin 2024; Dapagliflozin 2024; Empagliflozin 2024; Ertugliflozin 2024).***

Alpha-glucosidase inhibitors	
Acarbose	• Administer with the first bite of each main meal (at the start of each main meal) ***(Acarbose 2024).***
Glucagon-like peptide-1receptor agonists (GLP-1RAs)	
Semaglutide	• Administer on an empty stomach, ≥ 30 minutes before the first food, beverage, or other oral medications of the day with ≤120 ml of plain water only ***(Semaglutide 2024).*** • Eating should be started 30 to 60 minutes after the dose. Swallow tablets whole; do not split, crush, or chew ***(Semaglutide 2024).***

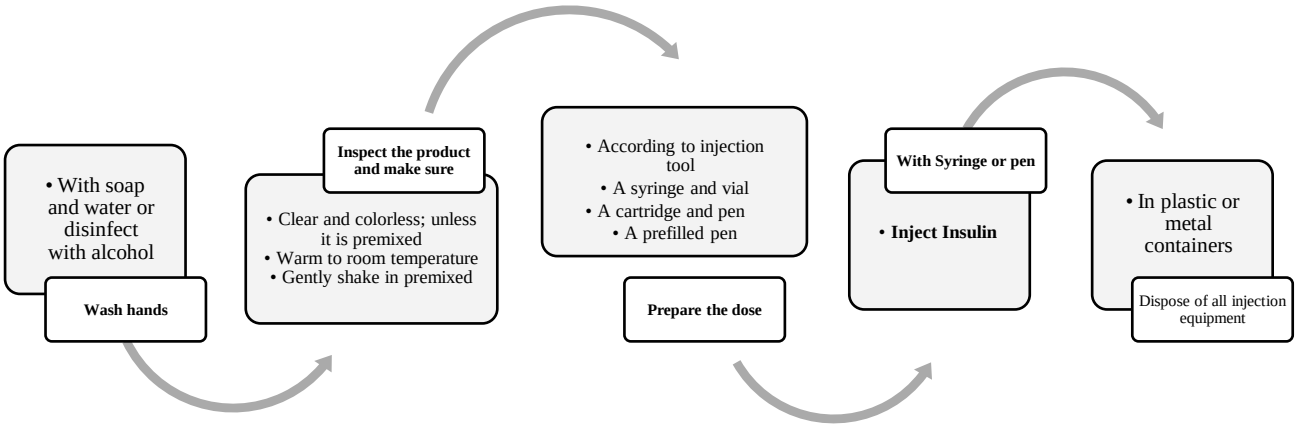
Table (6) Administration of Injectable Diabetic Medications

Injectable Medications	
Medication	**Administration**
Glucagon-like peptide-1 receptor agonists (GLP-1RAs): This group has general and specific instructions for the administration of each medication. **The general instructions are** ***(Dulaglutide 2024; Exenatide 2024; Liraglutide 2024; Semaglutide 2024):*** • Administer via Subcutaneous (SC) injection in the upper arm, thigh, or abdomen; rotate injection sites. • Do not inject intravenous (IV) or intramuscular (IM). • Do not mix with other products as insulin (administer as separate injections). Avoid adjacent injections if administering other agents in the same area of the body. **(N.B.):** There are prefilled pens consisting of a combination of insulin and GLP-1RAs such as Degludec/ Liraglutide prefilled pens, and Glargine/ Lixisenatide prefilled pens.	
Exenatide	- ***Immediate release***, use only if clear, colorless, and free of particulate matter. Administer within 60 minutes before morning and evening meals (or before the 2 main meals of the day, approximately ≥ 6 hours apart) ***(Exenatide 2024).*** • Set up each new pen before the first use by priming it as done with insulin administration *"See educational material No (5)"* • See the pen user manual for further details ***(Exenatide 2024).*** • Dial the dose into the dose window before each administration ***(Exenatide 2024).*** - ***Extended-release*** may be administered without regard to meals or time of day, it is a single-dose device that **does not** require priming before injection ***(Exenatide 2024).***
Dulaglutide	• Administer once weekly on the same day each week, without regard to meals or time of day ***(Dulaglutide 2024).*** • The day of weekly administration may be changed, as long as the last dose was administered ≥ 3 days before ***(Dulaglutide 2024).*** • Dulaglutide is a single-dose device that does ***not*** require priming before injection ***(Dulaglutide 2024).***

Liraglutide	• Administer without regard to meals or time of day ***(Liraglutide 2024)***. • Use only if clear, colorless, and free of particulate matter. Do not share pens between patients even if the needle is changed ***(Liraglutide 2024).*** • For each new prefilled pen (according to manufacturer's instructions) prime the needle before the first injection by turning the dose selector to the flow check symbol and injecting it into the air (priming is not required for subsequent injections) ***(Liraglutide 2024).*** • Use a new needle for each injection. Once injected, continue to depress the button until the dial has returned to zero and for an additional six seconds. Then, remove the needle ***(Liraglutide 2024).***
Semaglutide	• Administer with or without food at any time of day on the same day each week. The solution should be clear; do not use it if particulate matter and coloration are seen ***(Semaglutide 2024).*** • If changing the administration day is necessary, allow ≥ 48 hours between 2 doses ***(Semaglutide 2024).*** • According to the manufacturer's instructions, for each new prefilled pen, prime the needle before the first injection by turning the dose selector to the flow check symbol and injecting it into the air (priming is not required for subsequent injections) ***(Semaglutide 2024).*** • Use a new needle for each injection. Once injected, continue to depress the button until the dial has returned to zero and for an additional six seconds. Then, remove the needle from the skin ***(Semaglutide 2024).***

Insulin products

- Counsel the patient to administer insulin before eating or sometimes after it for a certain period depending on the beginning of the drug's action because some types are related to a specific time before eating or sometimes after it (such as 5, 15, 30 minutes). Injecting insulin at the appropriate time is the most effective way to control glucose levels after eating.
- Counsel the patients to the following instructions to inject insulin SC properly: *See education material No (5)*



Combinations of insulin and glucagon-like peptide-1 receptor agonists: This group had general and specific instructions. **The general instructions are** ***(Insulin degludec and liraglutide 2024; Insulin glargine and lixisenatide 2024):*** • Cold injections should be avoided (i.e. avoid injection after direct release from the refrigerator). • For SC use only. Do not administer IM, IV, or via an insulin pump. • Inject into the abdomen, thigh, or upper arm. Rotate injection sites for each dose; do not use the same site for each injection to avoid lipodystrophy or localized cutaneous amyloidosis. • Rotating from an injection site where lipodystrophy/cutaneous amyloidosis is present to an unaffected site may increase the risk of hypoglycemia. • Solution should appear clear and colorless; do not use if particulate matter or coloration is seen. • Do not split the dose. • Do not mix or dilute with any other insulin or solution. • Prefilled pen dials in 1-unit increments. For the prefilled pen, prime the needle before each injection with 2 units of medication (use a new needle for each injection).	
Degludec/liraglutide prefilled pens	• Administer once daily at the same time each day with or without food ***(Insulin degludec and liraglutide 2024).*** • Once injected, continue to depress the button until the dial has returned to zero and for an additional six seconds. Then, remove the needle ***(Insulin degludec and liraglutide 2024).***
Glargine/lixisenatide prefilled pens	• Administer within one hour before the first meal of the day, preferably the same meal each day ***(Insulin glargine and lixisenatide 2024).*** • Once injected, continue to depress the button until the dial has returned to zero and for an additional 10 seconds. Then, remove the needle ***(Insulin glargine and lixisenatide 2024).***

- Counselling on the proper storage conditions and ensuring insulin effectiveness, e.g., insulin may be expired or denatured. Advise the patient to recheck before reuse. Insulin storage conditions vary according to the dosage form (vial, cartridge, pen), type, and brand name. So, package inserts should be checked for each product. The following storage conditions represent the most common conditions ***(Center for Drug Evaluation and Research, 2017)***:

Table (7) Common Storage Conditions for Insulin

Storage Condition	Temperature	Not in Use	In Use
Room temperature	< 30 °C	Expires after 1 month	Expires after 1 month
Refrigerator	2 – 8 °C	Valid for use till the expiration date	Insulin products should not be refrigerated while in use.

- Insulin products should not be frozen; frozen insulin products should be discarded and not used ***(Center for Drug Evaluation and Research, 2017)***.
- Insulin products should be kept away from direct sunlight and heat ***(Center for Drug Evaluation and Research, 2017)***.
- Insulin in intravenous bags can be refrigerated (2 – 8 °C) for 48 hours and can be used at room temperature (< 30 °C) for an additional 48 hours (***HUMULIN R 2022).***Counselling patients who take approximately the same amount of insulin at the same time each day should eat meals at the same times, this helps prevent low blood sugar. This also applies to people who take pills that increase insulin levels, such as sulfonylureas. While, patients who take medications that do not usually cause low blood sugar, such as metformin, do not have to

follow this rule. However, children and some adults cannot control the frequency and quantities of food, so patients and their relatives should be counseled to refer to their physician to calculate the insulin/carbohydrate ratio (ICR) and insulin sensitivity factor (ISF) ***(Delahanty et al., 2024).***

- In this section, an overview of ICR and ISF (to present comprehensive information)

Table (8) ICR and ISF Overview

	ICR	ISF
Definition	• How many grams of carbohydrate are covered or disposed of by 1 unit of insulin ***(Diabetes Teaching Center at UCSF, 2011).*** • ICR can change depending on the time of day and can be influenced by stress, illness, and changes in physical activity ***(Delahanty et al., 2023).***	• In simple words, it shows how many "mg/dL" of blood glucose, can be lowered by one unit of insulin ***(Delahanty et al., 2023; Diabetes Teaching Center at UCSF, 2011).***
Aim	• To improve diabetes control, avoid hypoglycemia, and lower HbA1C ***(Delahanty et al., 2023; Raveendran, 2018).*** • To help in adjusting the mealtime dose of insulin ***(Delahanty et al., 2023; Raveendran, 2018).***	• To adjust insulin doses for hyperglycemia before or between meals ***(Delahanty et al., 2023).***
Methods used to calculate	**450/500 rule:** ICR can be calculated as follows ***(Delahanty et al., 2023):*** • For regular insulin, ICR = 450 divided by the total daily dose (TDD) of insulin. • For rapid-acting insulin, ICR = 500 divided by TDD of insulin. • Example: If the TDD is 100 units and the patient uses a regimen with rapid-acting insulin, then ICR= 500 / 100 = 5 **(i.e., ICR= 1:5, each unit of rapid insulin should cover approximately 5 g of carbohydrate).**	**1500/1800 rule:** ISF can be calculated as follows ***(Delahanty et al., 2023):*** • For regular insulin, divide 1500 by TDD. • For rapid-acting insulin, divide 1800 by TDD. • **Example:** If a patient has TDD of 60 units of rapid-acting insulin, and has a pre-meal glucose of 190 mg/dL. His pre-meal blood glucose target is 100 mg/dL. Then, how many units of insulin are required to maintain a patient's blood glucose in the target? • ISF=1800/60 = 30 • **(i.e., 1 unit of insulin is sufficient for every 30 mg/dL reduction in BG).** • Since the patient has 90 mg/dL more than the target, then the person should take an extra 3 units of rapid-acting insulin to correct to the target plus the number of units required to cover the carbohydrates consumed.
	Individually recorded data (more accurate than the 450/500 rule) ***(Delahanty et al., 2023):*** • Counsel the patient on how to record the time of meals and snacks, the amount and kind of food ingested, the amount of carbohydrates consumed, insulin dosages, physical	

	activity, and glucose monitoring results. • Counsel the patient to consume regular amounts of carbohydrates at meals and snacks so that pre- and postprandial glucose testing results can be used to match baseline insulin requirements to carbohydrate intake.	

- **Improving Medication Adherence through the following actions**
  - **Pharmacist—physician collaborative care model:** Pharmacists can enhance drug management by improving communication with the physician if there is any concern after medication review ***(Al Assaf et al., 2022; Hughes et al., 2017).***
  - **Family support:** It focuses on the involvement of the family during education and counseling to improve medication adherence ***(Al Assaf et al., 2022).***
  - **Psychosocial support:** It improves long-term medication compliance. Counsel the patient to refer to a specialist if he/she needs this ***(Hughes et al., 2017).***
  - **Simplifying complex medication regimes:** To avoid and overcome the problem of non-compliance ***(Al Assaf et al., 2022).***

▪ **<u>Other roles of pharmacists in PHC setting</u>**

- Medication reconciliation considering proper documentation ***(Thoma, 2013).***
- Pharmacists can participate in awareness campaigns to increase the awareness of all people to implement healthy lifestyles to prevent or delay T2DM. These educational campaigns should generally include the following topics but are not limited to:

  - Importance of physical activity ***(Blum et al., 2021; Delahanty et al., 2023; Delahanty et al., 2024; ElSayed et al., 2023c; Raveendran, 2018; Riddell et al., 2024).***
  - Importance of weight management ***(Blum et al., 2021; ElSayed et al., 2023b; Evert et al., 2019; Raveendran, 2018).***
  - Healthy diet ***(Evert et al., 2019).***
  - Importance of smoking cessation. Smoking is a risk factor for acquiring type 2 diabetes, it can also hasten the progression of the disease ***(Aas et al., 2023; Blum et al., 2021; ElSayed et al., 2023d).***
  - Importance of sleep hygiene. Proper sleep is essential for the body's regular metabolic and hormonal functions. Sleep deprivation and poor sleep quality result in altered metabolic and hormonal activity, which leads to the development of T2DM. People who sleep less than 6 hours per night are at risk of getting diabetes, and 7 hours of undisturbed sleep per night is recommended ***(Amin et al., 2017; Pamidi & Tasali, 2012; Raveendran, 2018; Touma & Pannain, 2011).***

Barriers to Delivering Effective Community Pharmacist-Provided DM Service

- Increasing the integration of community pharmacists into interdisciplinary, collaborative teams focused on improving the population and lowering healthcare costs provides a significant opportunity to promote care value ***(Newman et al., 2019).*** Community pharmacists are in a unique position to provide significant patient care services to diabetic patients ***(Plake et al., 2007).*** Some pharmacists with sufficient knowledge about diabetes care do not deliver this service regularly, because of existing barriers to care other than knowledge and skills ***(Plake et al., 2007).***
- Pharmacists should assess the existence of these barriers when providing diabetes services and recognize strategies to overcome these obstacles to facilitate the delivery of diabetes services ***(Al Haqan et al., 2017; Newman et al., 2019).***
- Pharmacists who perform their role following the rules and guidelines of good practice and those who are keen to acquire continuing professional development and increase their capabilities, gain the full trust of patients and other healthcare providers. As they prove to be helpful and their substantial role is confirmed ***(Al Haqan et al., 2017; Wang et al., 2021).***
- Several barriers hinder community pharmacists' uptake and delivery of healthcare services. These barriers include, but are not limited to, the following:

Barriers to effective patient counseling and tips to overcome	**Lack of convenient space for counseling:** Some solutions include the use of temporary structures to distinguish between the dispensing area and counseling area or provide the counseling by telephone ***(Al Haqan et al., 2017; Blum et al., 2021; Wang et al., 2021).***
	Insufficient time and a heavy workload: Pharmacists may use already prepared materials from accredited resources and refer to online sources of clinical information ***(Blum et al., 2021; Breiner, 2020; Plake et al., 2007; Wang et al., 2021).*** Examples include approved patient education materials from the **Centers for Disease Control and Prevention** (CDC), http://Diabetes.UK, and other scientific associations. Also, pharmacists may use the patient counseling materials included in the annexes to this manual. Lexicomp and uptodate (patient's education section, Arabic language) are also useful tools.
	Accreditation and training: Participating in training events such as seminars, conferences, symposia, and continuing professional development programs helps to educate and provide pharmacists with an efficient service. As a result, maintaining an approach to continuing learning among pharmacists benefits both pharmacists and patients in better management and prevention of complications for diabetic patients ***(Al Haqan et al., 2017; Blum et al., 2021; Newman et al., 2019; Wang et al., 2021).*** EDA provides training webinars free of charge for community pharmacists regularly. You may follow the EDA official website to get informed about webinar registration and attendance.
	Information technology (IT) infrastructure: IT systems present constraints that limit the involvement of community pharmacists in clinical care delivery. Data in community pharmacy IT management systems are generally limited to medication dispensing. So, developing health information systems that enable the exchange of patient health information is critical to integrating community pharmacists into multidisciplinary care teams. Electronic health records are a future promising project that allows pharmacists and other healthcare providers to communicate effectively regarding patients' information ***(Newman et al., 2019).***
	Patient attitudes and cultural/language barriers: Pharmacists should be trained to communicate effectively with patients of different attitudes and social backgrounds ***(Plake et al., 2007; Wang et al., 2021).***

Illustration (2) Barriers and Potential Solutions for Community Pharmacist-Provided DM Service

Inpatient Settings

Clinical Pharmacists' Roles in Diabetic Patient Care

Inpatient settings: Clinical Pharmacists' Roles in Diabetic Patient Care

- Pharmacists working in hospital settings are encountered with out-patient, which is already discussed in the ambulatory care section, and in-patient care which include patient-oriented duties that are done by the clinical pharmacists and dispensing duties. The clinical pharmacist's duties for patient care are discussed here while the pharmacist's dispensing duties are not discussed in this guide.
- Clinical pharmacists collaborate closely with physicians, other healthcare providers, and patients to ensure that the medications recommended for them contribute to the greatest potential health outcomes. Clinical pharmacists work in healthcare environments where they contact physicians and other health professionals regularly, which helps to improve care coordination ***(ACCP, 2023).***
- Clinical pharmacists should have sufficient education and training before starting their roles and responsibilities ***(ACCP, 2023).***

- **<u>Clinical pharmacists' role includes the following</u>:**
  - Performing patient reconciliation ***(Thoma, 2013).***
  - Assessing the patient's health conditions and determining whether the prescribed medications are ideally addressing the patient's needs and goals of care ***(ACCP, 2023).***
  - Checking the patient's drugs for appropriateness and efficacy ***(ACCP, 2023).***
  - Recognizing untreated medical issues that could be improved or resolved with adequate medication therapy ***(ACCP, 2023).***
  - Following the patient's progress to assess the effects of the patient's drug medications on the patient's health ***(ACCP, 2023).***
  - Consulting with the patient's physicians and other healthcare professionals to determine which drug therapy best fulfills the patient's needs and contributes to the overall therapeutic goals ***(ACCP, 2023).***
  - Counseling the patient on proper medication administration ***(ACCP, 2023).***
  - Supporting the efforts of the healthcare team to educate the patient on other vital activities to enhance or maintain health, such as exercise, diet, and preventive measures such as immunization ***(ACCP, 2023).***
  - Advising the patient to seek medical attention from doctors or other healthcare professionals as needed ***(ACCP, 2023).***

- **Clinical pharmacists must be aware of a variety of facts and information to carry out their duties and responsibilities in diabetes patient care as stated in the following chapters.**

Criteria for Diagnosis

- Diagnosis is led by physicians, yet we added this section to provide a brief overview for the clinical pharmacist of this aspect of physician responsibilities, for the comprehensive delivery of clinical information.
- Plasma glucose criteria should be used to diagnose diabetes in conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies such as sickle cell disease, hemodialysis, pregnancy (second and third trimesters and the postpartum period), recent blood loss or transfusion, glucose-6-phosphate dehydrogenase deficiency, Human Immunodeficiency Virus (HIV), or erythropoietin therapy ***(ElSayed et al., 2023f).*** **(B)**

Table (9) Criteria for Diagnosis of Gestational Diabetes Mellitus adapted from *(ElSayed et al., 2023f)*

Gestational Diabetes Mellitus "GDM"	
One-step strategy	- A 75-g oral glucose tolerance test "OGTT" is performed with plasma glucose measurement when the patient is fasting and at 1 and 2 hours at 24-28 weeks of gestation in people who have never had diabetes. - After an overnight fast of at least 8 hours, the OGTT should be conducted in the morning. - GDM is diagnosed when any of the following plasma glucose levels are reached or exceeded: • Fasting: 92 mg/dL • 1 h: 180 mg/dL • 2 h: 153 mg/dL
Two-step strategy	**Step 1** - At 24-28 weeks of gestation, in individuals not previously diagnosed with diabetes, do a 50-g glucose load test "GLT" (non-fasting), with plasma glucose measurement at 1 hour. - If the plasma glucose level measured 1 hour after the load is ≥130, 135, or 140 mg/dL, a 100-g OGTT is performed. **Step 2** - When the patient is fasting, the 100-g OGTT should be conducted. - GDM is diagnosed when at least ***two**** of the four plasma glucose levels (measured fasting and at 1, 2, and 3 h during the OGTT) are reached or exceeded: *"American College of Obstetricians and Gynecologists notes that ***one*** elevated value can be used for diagnosis" • Fasting: 95 mg/dL • 1 h: 180 mg/dL • 2 h: 155 mg/dL • 3 h: 140 mg/dL

Table (10) Criteria for Diagnosis of Diabetes Mellitus and Prediabetes

	Diabetes ***(Blum et al., 2021; ElSayed et al., 2023f; Mutlaq, 2020)*** In the absence of explicit hyperglycemia, two abnormal test findings at the same time (e.g., A1C and FPG) or at two different time points are required for diagnosis "i.e.diagnosis requires confirmatory testing" **(A)**	**Prediabetes** ***(Blum et al., 2021; ElSayed et al., 2023f; Mutlaq, 2020)*** The risk of developing diabetes from prediabetes is apparent in the readings of the three tests (A1C, FPG, PPG), taking into consideration that the readings near upper limits are associated with higher risk.
A1C	≥ 6.5% **(A)**	5.7 – 6.4% **(B)**
Or		
Fasting plasma glucose (FPG) (fasting is defined as not consuming any calories for at least 8 hours)	≥126 mg/dL **(A)**	Impaired fasting glucose (IFG): FPG 100 - 125 mg/dL **(B)**
Or		
2-hr post prandial plasma glucose (2-hr PPG)	2-h PPG ≥200 mg/dL during (OGTT)* **(A)** "The test should be performed according to WHO guidelines, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water"	Impaired glucose tolerance (IGT): 2-h PPG during 75-g OGTT* 140-199 mg/dL **(B)**
Or		
Random plasma glucose (RPG) + Symptoms	RPG ≥200 mg/dL in a patient with characteristic hyperglycemia symptoms (polydipsia or polyuria) or signs of catabolism (weight loss) or hyperglycemic crises. **(A)**	

*Adequate carbohydrate consumption (at least 150 g/day) should be maintained for three days before oral glucose tolerance testing as a diabetes or prediabetes screening test. **(A)**

Glycemic Goal/Target

- Measurements of A1C, blood glucose meters (BGM) by capillary (finger-stick) devices, and continuous glucose monitoring (CGM) using time in range (TIR) and mean glucose are used to assess the glycemic status ***(ElSayed et al., 2023e).***
- Individual patients may require more or less severe glycemic targets. Individualized goals should be set based on diabetes duration, age/life expectancy, concomitant diseases, known cardiovascular disease (CVD) or advanced microvascular problems, hypoglycemia unawareness, and specific patient concerns ***(Blum et al., 2021; ElSayed et al., 2023e).***
- If A1C targets are not accomplished despite meeting preprandial glucose goals, postprandial glucose test may be requested and measured 1-2 hours after the start of the meal, as these are often peak values in diabetics ***(ElSayed et al., 2023e).***
- Recommendations ***(ElSayed et al., 2023e):***
  - Assess glycemic status twice a year using appropriate A1C and continuous glucose monitoring metrics. For individuals who are not meeting treatment goals, whose therapy has recently changed, who have frequent or severe hypoglycemia or hyperglycemia, changing health status, or who are experiencing growth and development problems, assess more frequently (e.g., every 3 months). **(E)**
  - CGM is indicated for older persons with type 1 diabetes to minimize hypoglycemia. **(A)**
  - CGM should be considered for older persons with type 2 diabetes who take several daily insulin doses to enhance glycemic outcomes and decrease glucose variability. **(B)**

Table (11) Glycaemic Targets

	A1C	Fasting/Preprandial capillary plasma glucose	Peak postprandial capillary plasma glucose	Bedtime glucose
Non-pregnant adults ***(ElSayed et al., 2023e)***	• **< 7.0%** is appropriate when it is achieved without significant hypoglycemia. **(A)** • Less stringent glycemic goals may be appropriate for individuals with limited life expectancy or where the harms of treatment are greater than the benefits. **(B)**	• 80–130 mg/dL	• <180 mg/dL • If **A1C** goals are **not** met despite **meeting preprandial** glucose goals, **postprandial** glucose targets may be **considered.** • In persons with diabetes, postprandial glucose measures should be taken 1-2 hours after the start of the meal, when levels are often at their peak.	–
In older people, a lower A1C goal may be set for an individual if it is achieved without recurrent or severe hypoglycemia or unnecessary treatment burden ***(ElSayed et al., 2023g)***				

Healthy older adults (few comorbid chronic conditions, normal cognitive and functional status)	• < 7.0 –7.5% **(C)**	• 80 –130 mg/dL	–	• 80 –180 mg/dL
Complex/ intermediate health older adults (multiple chronic illnesses* or two or more impairments in instrumental activities of daily living (ADL) or mild-to-moderate cognitive impairment)	• Individualize glycemic target • <8.0% for individuals with cognitive and functional difficulties, frailty, severe comorbidities, and a lower risk-to-benefit ratio for diabetic medicines. **(C)**	• 90–150 mg/dL	–	• 100–180 mg/dL
Very complex/poor health older adults (long-term care (LTC) or end-stage chronic illnesses** or moderate to severe cognitive impairment or two or more ADL deficits)	• Avoid relying on A1C; instead, make glycemic control decisions based on avoiding hypoglycemia and symptomatic hyperglycemia. **(C)**	• 100–180 mg/dL	–	• 110–200 mg/dL
Pregnant ***(ElSayed et al., 2023h)***	• The ideal A1C target in pregnancy is < **6%** if attained without substantial hypoglycemia, but this target might be modified to < **7%** if necessary to avoid hypoglycemia.*** ** (B)**	• Fasting, and preprandial, and postprandial blood glucose monitoring are recommended in individuals with diabetes in pregnancy to achieve optimal glucose levels. Glucose goals are FPG <95 mg/dL and either 1-hr PPG <140 mg/dL or 2-hr PPG <120 mg/dL. **(B)**		

Hospitalized patients ***(ElSayed et al., 2023i)*** "Insulin **(A)** and other therapies **(B)** should be initiated for the treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (confirmed on two occasions within 24 h) for noncritically ill individuals. **(A)"**	—	• Once therapy is initiated, most critically ill patients should have a target glucose range of **140 -180 mg/dL**. **(A)** • More strict targets, such as **110 -140 mg/dL**, may be appropriate for certain critical patients and are acceptable if met without substantial hypoglycemia. **(B)** • A target range of **100-180 mg/dL** for non-critically sick patients with "new" hyperglycemia as well as people with diabetes before admission for inpatient management of hyperglycemia in non-critical care. • Fasting glucose levels **below 100 mg/dL** have been demonstrated to predict hypoglycemia within the next 24 hours. • Certain populations can tolerate glycemic levels up to **250 mg/dL** (terminally ill individuals with short life expectancy, advanced kidney failure, and/or dialysis, and/or labile glycemic excursions).

***** Arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, chronic renal disease (stage 3 or worse), myocardial infarction, and stroke are all examples of coexisting chronic illnesses. "Multiple" implies at least three, although many patients have five or more.

****** The presence of a single end-stage chronic illness, such as stage 3-4 heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, can cause significant symptoms or impairment of functional status, reducing life expectancy significantly. For diabetes therapy in patients with advanced disease, ***different patient classifications have been proposed as follows***:

1. **A stable patient:** Continue the person's existing regimen, with a focus on hypoglycemia avoidance and hyperglycemia management through blood glucose testing, keeping glucose levels below the renal threshold of glucose, and hyperglycemia-mediated dehydration. A1C monitoring plays no role.

2. **A patient with organ failure:** The most important aspect is to avoid hypoglycemia. Dehydration must be avoided and managed. Insulin treatment should be lowered but not stopped in persons with type 1 diabetes as their oral meal intake falls. Agents that may cause hypoglycemia should be lowered in dose for persons with type 2 diabetes. The primary goal is to avoid hypoglycemia, allowing for glucose values in the upper level of the desired target range.

3. **A dying patient:** Because dying people with type 2 diabetes are unlikely to consume any oral drugs, discontinuing all medications may be a reasonable option. There is no consensus in persons with type 1 diabetes, however, a small quantity of basal insulin may maintain glucose levels and prevent acute hyperglycemic consequences.

******* A1C is slightly lower in pregnant women with and without diabetes due to higher red blood cell turnover. As a result, it should be used as a secondary indicator of glycemic outcomes in pregnancy, after blood glucose monitoring

Management Approaches for Adults

Considerations for GDM Treatment *(ElSayed et al., 2023j)*

- Insulin is the medicine of choice for GDM therapy. Metformin and glyburide should not be used as first-line medications since they both penetrate the placenta and reach the fetus. Metformin should be stopped by the end of the first trimester when used to treat polycystic ovary syndrome and induce ovulation. **(A)**
- Long-term safety data for other oral and non-insulin injectable glucose-lowering medicines are lacking. **(E)**

Considerations for Prediabetes Treatment *(ElSayed et al., 2023j)*

- Individuals with prediabetes who are overweight or obese and have a history of gestational diabetes mellitus should undergo extensive lifestyle treatments and/or metformin to prevent diabetes. **(A)**

Approach to Diabetes Type 1 Treatment *(ElSayed et al., 2023j)*

- There are various approaches to insulin treatment. Still, the central precept in the management of type 1 diabetes (T1DM) is that some form of insulin is given in a planned regimen tailored to the individual to keep them safe and out of diabetic ketoacidosis, as well as to avoid significant hypoglycemia, with every effort made to reach the individual's glycemic targets.
- Individual preferences, cost, insulin type, dosing routine, and self-management capabilities should all be addressed when selecting an insulin delivery system.
- Insulin replacement therapy typically consists of basal insulin *(that works steadily throughout the day, frequently referred to as "background" insulin)*, and bolus insulin *(a single dose of insulin, given for a meal or correction)*. Mealtime insulin *(insulin doses with a meal)*, and corrective insulin *(insulin is given when the blood glucose level is too high and needs to be adjusted "lowered").*
- Basal insulin consists of intermediate-acting insulin-neutral protamine Hagedorn (NPH) insulin and long-acting insulin analogs (LAA). Mealtime and corrective insulin consist of rapid-acting insulin analogs (RAA), ultra-rapid-acting insulin analogs (URAA), and short-acting regular insulin (R).
- The long-acting basal dose is titrated to control overnight and fasting glucose. A well-timed injection of prandial insulin is the most effective way to control postprandial glucose excursions.
- To lower the risk of hypoglycemia, most people with type 1 diabetes should take insulin analogs over injectable human insulins. **(A)**
- Continuous glucose monitoring (CGM) reduces hypoglycemia and improves glycemic outcomes and quality of life in adults with T1DM. **(B)**
- CGM improves glycemic outcomes and reduces hypoglycemia in older persons on insulin therapy with T1DM, **(A)** and for older persons with type 2 diabetes. **(B)**
- To avoid diabetic ketoacidosis, elderly persons with T1DM require some form of basal insulin even when they are unable to eat.
- In older persons, it may be beneficial to administer insulin after meals to ensure that the dose is appropriate for the quantity of carbohydrates taken in the meal.

Educate and Counsel Patients about……
(Check the pharmacists' roles in diabetic patient care at outpatient setting for more details)

- ***Educate*** the patient/caregiver about target glucose levels.
- ***Educate*** the patient/caregiver on the significance of lifestyle changes and co-morbidity management.
- ***Educate*** the patient/caregiver on critical signs/symptoms that require immediate attention, such as trouble breathing, a low level of consciousness, or rapid breathing with fruity-smelling breath, etc.
- ***Educate*** the patient/caregiver on the importance of drug adherence in avoiding macro/micro-complications.
- ***Educate*** the patient/caregiver on recognizing and dealing as a first aid with acute complications.
- ***Educate*** the patient/caregiver that weight loss when eating properly might be an indicator of hyperglycemia.
- ***Educate*** the patient/caregiver on the meaning of a sick day and how to manage diabetes during these times, as the patient should be advised to continue taking diabetes medications as prescribed, including insulin, to keep monitoring of blood glucose levels on a regular basis (e.g., every four hours), to drink plenty of (calorie-free) drinks to avoid dehydration, to eat properly, and to check temperature every morning and evening to determine a fever.
- ***Counsel*** patients to refer to their physician to correct insulin based on hyperglycemia present, glycemic target, sick-day management, and predicted physical activity ***(ElSayed et al., 2023i).*** **(B)**
- ***Counsel*** to adhere to physician instructions about adjusting insulin doses at mealtime based on carbohydrate intake, fat and protein composition, and predicted physical activity ***(ElSayed et al., 2023i).*** **(B)**
- ***Counsel*** the patient/caregiver on his/her type of insulin, dosages, efficacy, duration and time of administration, storage and stability, and self-monitoring blood glucose.
- ***Counsel*** the patient/caregiver on optimal delivery technique to optimise glucose control and insulin use safety, as well as proper injection site rotation and how to recognise and avoid areas of lipohypertrophy. In obese people, recent research supports the use of short needles (e.g., 4-mm pen needles) as more effective and well tolerated than longer needles. *"See educational material No (5)"*

Box (1) Patient Education and Counselling Tips for T1DM
(Blum et al., 2021; ElSayed et al., 2023c; ElSayed et al., 2023d; ElSayed et al., 2023e; ElSayed et al., 2023j; Mutlaq, 2020)

Management approach

Multiple daily injections (MDI) of prandial and basal insulin **(A)** "Typical multi-dose regimens combine pre meal use of shorter-acting insulins with a longer-acting formulation"	Insulin adjuvants with non-insulin treatment "Injectable and oral glucose lowering drugs"	Surgical treatment "Pancreas and islet transplantation"
MDI with LAA + RAA or URAA ***Less preferred:*** NPH + RAA or URAA NPH + R Two daily injection with NPH + R ***or*** premixed	Adjunctive agents' risks and benefits are still being assessed, with consensus statements providing recommendations on patient selection and precautions.	Pancreas transplantation is a surgical approach that is considered in some countries but not in Egypt, and it is reserved for people with T1DM who are undergoing simultaneous renal transplantation, following renal transplantation, or who have recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management due to the potential adverse effects of long-term immunosuppressive therapy.
▪ Generally, individuals require **50%** of their daily insulin as basal and **50%** as prandial, although this depends on a variety of factors, including whether the individual consumes lower or higher carbohydrate meals. ▪ Based on weight, total daily insulin requirements can be predicted, with usual doses ranging from **0.4 to 1.0 units/kg/day.** ▪ During pregnancy, and medical illness, higher amounts are required. ▪ In persons with type 1 diabetes who are metabolically stable, a typical starting dose is **0.5units/kg/day**, with **half** provided as prandial insulin to regulate blood glucose after meals and **the other half** as basal insulin to control glycemia between meal absorption.	**Metformin:** caused small reductions in body weight, and lipid levels, and insulin dose but did not improve A1C. **Glucagon-like peptide 1 receptor agonists (GLP-1 RAs):** "liraglutide 1.8 mg/daily" showed modest A1C reductions (~0.4%), weight loss (~5kg), and insulin dosage reductions. **Sodium–glucose cotransporter 2 (SGLT2) inhibitors:** is related with an increased risk of diabetic ketoacidosis, despite improvements in A1C, blood pressure and reduction in body weight.	

Illustration (3) Approach to Diabetes Type 1 Treatment ***(ElSayed et al., 2023j)***

LAA: Long-Acting Insulin Analogs, MDI: Multiple Daily Injections, NPH: Neutral Protamine Hagedorn, R: Regular Insulin, RAA: Rapid-Acting Insulin Analogs, URAA: Ultra-Rapid-Acting Insulin Analogs

Table (12) Characteristics of Various Regimens of Insulin adapted from *(ElSayed et al., 2023j)*

Injected insulin regimen	Flexibility	Reduced hypoglycemia risk	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less preferred			
NPH + RAA or URAA	++	++	++
NPH + R	++	+	+
Two daily injections with NPH + R *or* premixed	+	+	+

Table (13) Different Insulin Regimens Used adapted from *(ElSayed et al., 2023j)*

Regimen	Timing and distribution	Adjusting doses
Regimens that closely resemble natural insulin secretion		
MDI: LAA + flexible doses of URAA or RAA at meals	**LAA:** once daily (insulin detemir ***or*** insulin glargine may require twice daily dosing); generally, 30-50% of TDD **Mealtime and correction:** URAA ***or*** RAA based on ICR and/or ISF and target glucose.	**LAA:** Based on overnight or fasting glucose or daytime glucose outside of the exercise time course, or URAA or RAA injections. **Mealtime insulin:** If carbohydrate counting is reliable, ICR is adjusted if glucose levels after meals are consistently over the target. **Correction insulin:** If the correction does not regularly bring glucose into range, modify ISF and/or glucose target.
MDI regimens with less flexibility		
Four injections daily with fixed doses of NPH and RAA	**Pre-breakfast:** RAA ~ 20% of TDD. **Pre-lunch:** RAA ~ 10% of TDD. **Pre-dinner:** RAA ~ 10% of TDD. **Bedtime:** NPH ~ 50% of TDD.	**Pre-breakfast RAA:** depending on BGM after breakfast or before lunch. **Pre-lunch RAA:** depending on BGM after lunch or before dinner. **Pre-dinner RAA:** depending on BGM after dinner or at bedtime. **Evening NPH:** depending on fasting or overnight BGM.
Four injections daily with fixed doses of NPH and R	**Pre-breakfast:** R ~ 20% of TDD. **Pre-lunch:** R ~ 10% of TDD. **Pre-dinner:** R ~ 10% of TDD. **Bedtime:** NPH ~ 50% of TDD.	**Pre-breakfast R:** depending on BGM after breakfast or before lunch. **Pre-lunch R:** depending on BGM after lunch or before dinner. **Pre-dinner R:** depending on BGM after dinner or at bedtime. **Evening NPH:** depending on fasting or overnight BGM.

Regimens requiring fewer daily injections		
Three injections daily: NPH+R ***or*** NPH+RAA	**Pre-breakfast:** ~ 40% NPH + ~15% R ***or*** RAA. **Pre-dinner:** ~15% R ***or*** RAA. **Bedtime:** 30% NPH.	**Morning NPH:** Depending on pre-dinner BGM. **Morning R:** Depending on pre-lunch BGM. **Morning RAA:** Depending on post-breakfast ***or*** pre-lunch BGM. **Pre-dinner R:** Depending on bedtime BGM. **Pre-dinner RAA:** Depending on post-dinner ***or*** bedtime BGM. **Evening NPH:** Depending on fasting BGM.
Twice-daily "split-mixed": NPH+R ***or*** NPH+RAA	**Pre-breakfast:** ~ 40% NPH + ~15% R ***or*** RAA. **Pre-dinner:** ~30% NPH + ~15% R ***or*** RAA.	**Morning NPH:** Depending on pre-dinner BGM. **Morning R:** Depending on pre-lunch BGM. **Morning RAA:** Depending on post-breakfast ***or*** pre-lunch BGM. **Evening R:** Depending on bedtime BGM. **Evening RAA:** Depending on post-dinner ***or*** bedtime BGM. **Evening NPH:** Depending on fasting BGM.

ICR, insulin-to-carbohydrate ratio *(how many grams of carbohydrate 1 unit of insulin covers)* = **450 "for regular insulin" or 500 "for rapid insulin" ÷ TDD** but take care that **the insulin-to-carbohydrate ratio may vary during the day.**; **ISF**, insulin sensitivity factor *(how many" mg/dl" 1 unit of insulin lowers the blood glucose level)* = **1500 "for regular insulin" or 1800 "for rapid-acting insulin" ÷ TDD *(Diabetes Teaching Center at UCSF, 2011; Delahanty et al., 2023)*; TDD**, total daily insulin dose.

ICR: insulin-to-carbohydrate ratio, LAA: Long-Acting Insulin Analogs, MDI: Multiple Daily Injections, NPH: Neutral Protamine Hagedorn, R: Regular Insulin, RAA: Rapid-Acting Insulin Analogs, TDD: Total Daily Dose URAA: Ultra-Rapid-Acting Insulin Analogs

Diabetes Type 2 Treatment Approach

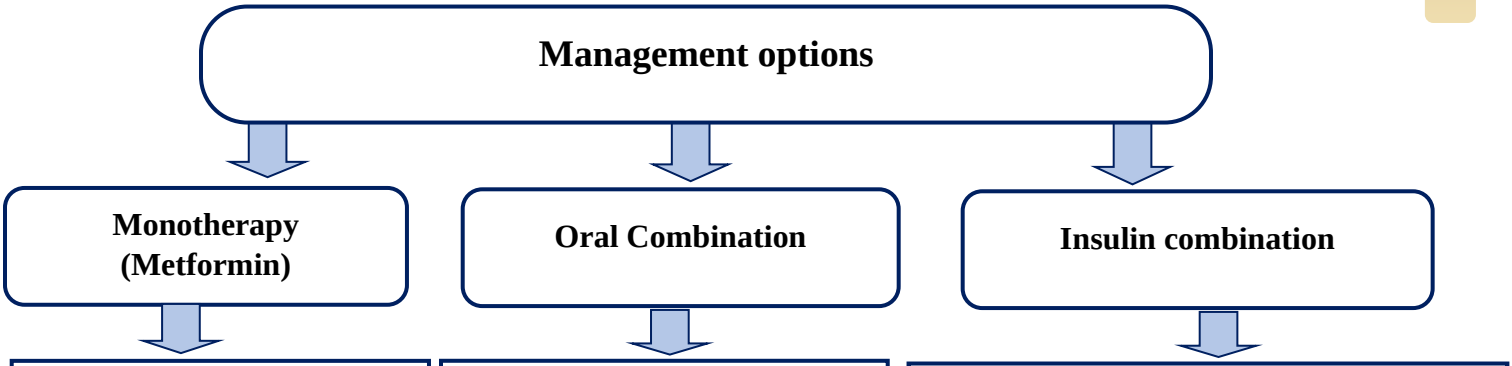
- Treatment regimens must be reassessed regularly for efficacy, adverse effects, and burden. Because of ineffectiveness, intolerable side effects, expense, or a change in glycemic goals as a result of the development of comorbidities or changes in treatment goals, the individual will require medication reduction, intensification, or discontinuance ***(ElSayed et al., 2023j).***
- Healthy lifestyle behaviors, diabetes self-management education and support (DSMES), clinical inertia *"the failure to start a therapy or its intensification/de-intensification when appropriate"* (***Andreozzi et al., 2020)*** avoidance, and social determinants of health should all be considered in type 2 diabetes glucose-lowering management ***(ElSayed et al., 2023j).*** **(A)**
- Person-centered therapeutic considerations, such as comorbidities, treatment goals, risk of adverse reactions and tolerability, hypoglycemia risk, impact on weight, cost, and accessibility, and personal preferences should guide the selection of pharmacologic therapy ***(ElSayed et al., 2023j).*** **(E)**
- Medication regimens and medication-taking behavior should be reviewed regularly (every 3-6 months) and changed as needed to account for specific characteristics that influence treatment selection ***(ElSayed et al., 2023j).*** **(E)**
- Treatment modification recommendations for persons who are not meeting treatment goals should not be postponed ***(ElSayed et al., 2023j).*** **(A)**
- The glucose-lowering treatment strategy should include techniques that help persons with type 2 diabetes achieve their weight-management goals ***(ElSayed et al., 2023j).*** **(A)**
- People with type 2 diabetes who have not met their specific weight goals may consider additional weight management therapies "e.g., escalation of lifestyle adjustments, organized weight management programs, pharmacologic medications, or metabolic surgery, as appropriate" ***(ElSayed et al., 2023j).*** **(A)**
- Pharmacologic methods with appropriate efficacy to accomplish and sustain treatment goals, such as metformin or other medications, including combination therapy, should be considered ***(ElSayed et al., 2023j).*** **(A)**
- In adults with type 2 diabetes who have not reached their specific glycemic objectives, the next glucose-lowering drug should be chosen keeping the individualized glycemic and weight goals in mind, as well as the presence of other metabolic comorbidities and the risk of hypoglycemia ***(ElSayed et al., 2023j).*** **(A)**
- People with type 2 diabetes who have an established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease should be treated with cardio-renal risk-lowering medications independent of A1C and in consideration of person-specific factors ***(ElSayed et al., 2023j).*** **(A)**
- SGLT2 inhibitor is recommended for people with type 2 diabetes who have HF (with reduced or preserved ejection fraction) to improve glycemic control and prevent HF hospitalizations ***(ElSayed et al., 2023j).*** **(A)**
- People with type 2 diabetes who have CKD (eGFR 20-60 mL/min per 1.73 m2 and/or albuminuria) should use an SGLT2 inhibitor to minimize CKD progression, cardiovascular events, and hospitalizations for HF. However, the glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min per 1.73 m^2 ***(ElSayed et al., 2023j).*** **(A)**
- People with type 2 diabetes and advanced CKD (eGFR <30 mL/min per 1.73 m2) should use a GLP-1 RA for glycemic management since it reduces the risk of hypoglycemia and cardiovascular events ***(ElSayed et al., 2023j).*** **(B)**
- People without risk factors, The treatment goal is weight management and controlling blood sugar levels ***(ElSayed et al., 2023j).*** **(A)**
- When insulin used at any stage of T2DM, clinicians should be aware of the risk of insulin overbasalization. Clinical signals of overbasalization **include** a basal dose more than ~0.5 units/kg/day, hypoglycemia (aware or unaware), large bedtime -morning glucose or or postprandial-

to-preprandial glucose differential (e.g., bedtime–morning glucose differential ≥ 50 mg/dL), and excessive glycemic variability. Overbasalization should induce reevaluation in order to further personalise therapy. When overbasalization is suspected, a comprehensive reevaluation should be conducted right away to further customize therapy to the individual's needs ***(ElSayed et al., 2023j).*** **(E)**

Educate and Counsel Patients about……
(Check the pharmacists' roles in diabetic patient care at outpatient setting for more details)

- ***Educate*** the patient/caregiver about target glucose levels.
- ***Educate*** the patient/caregiver on the significance of lifestyle changes and co-morbidity management.
- ***Educate*** the patient/caregiver on critical signs/symptoms that require immediate attention, such as trouble breathing, a low level of consciousness, or rapid breathing with fruity-smelling breath, etc.
- ***Educate*** the patient/caregiver on the importance of drug adherence in avoiding macro/micro-complications.
- ***Educate*** the patient/caregiver on recognizing and dealing as a first aid with acute complications.
- ***Educate*** the patient/caregiver that ***w***eight loss when eating properly might be an indication of hyperglycemia.
- ***Educate*** the patient/caregiver on the meaning of a sick day and how to manage diabetes during these times, as the patient should be advised to continue taking diabetes medications as prescribed, including insulin, to keep monitoring of blood glucose levels on a regular basis (e.g., every four hours), to drink plenty of (calorie-free) drinks to avoid dehydration, to eat properly, and to check temperature every morning and evening to determine a fever.
- ***Counsel*** patients to refer to their physician to correct insulin based on hyperglycemia present, glycemic target, sick-day management, and predicted physical activity. **(B)**
- ***Counsel*** to adhere to physician instructions about adjusting insulin doses at mealtime based on carbohydrate intake, fat and protein composition, and predicted physical activity. **(B)**
- ***Counsel*** the patient/caregiver on his/her type of insulin, dosages, efficacy, duration and time of administration, storage and stability, and self-monitoring blood glucose.
- ***Counsel*** the patient/caregiver on optimal delivery technique to optimise glucose control and insulin use safety, as well as proper injection site rotation and how to recognise and avoid areas of lipohypertrophy. In obese people, recent research supports the use of short needles (e.g., 4-mm pen needles) as more effective and well tolerated than longer needles. *"See educational material No (5)"*

Box (2) Patient Education and Counselling Tips for T2DM
(Blum et al., 2021; ElSayed et al., 2023c; ElSayed et al., 2023d; ElSayed et al., 2023e; ElSayed et al., 2023j; Mutlaq, 2020)



- Metformin as first line therapy (unless contraindicated) has beneficial effects on A1C, weight neutral "potential for modest loss", does not cause hypoglycemia, and reduces cardiovascular mortality
- Metformin may be temporarily stopped before to surgeries, during hospitalisations, imaging studies uing contrast, and during acute sickness that may impair renal or liver function.

- Some patients may benefit from early combination therapy at the start of treatment to accelerate the achievement of individualized treatment goals. **(A)**
- In patients with A1C values 1.5-2.0% above goal, initial combination therapy should be explored.
  - If A1C > 7.5 %: start combination of 2 agents.
  - If A1C > 9% or >1.5% above the goal: start 2-3 agents.
- The addition of high-glycemic-efficacy medicines or cardiovascular /renal risk reduction therapies (e.g., GLP-1 RAs, SGLT2 inhibitors) may allow for weaning from the existing regimen, particularly of agents that may raise the risk of hypoglycemia. Thus, treatment intensification may not always be the result of a pure sequential addition of therapy, but rather of regimen modification per person-centered therapeutic goals.

- ***Early insulin administration should be considered.*** regardless of background glucose lowering therapy or disease stage if
  - There is persistent catabolism (unexpected weight loss), ***or***
  - Hyperglycemia symptoms are present, ***or***
  - A1C levels (>10%) ***or*** blood glucose (BG) levels (≥300mg) mg/dL. **(E)**
- GLP-1 RA are favored over insulin in adults with type 2 diabetes. **(A)**
- Combination therapy with **GLP-1 RA** is indicated for improved efficacy, as well as reduce weight and hypoglycemia risk. Insulin dosing should be evaluated after adding or increasing the dose of GLP-I RA. **(A)**
- Glucose lowering agents should be continued upon starting insulin therapy (unless contraindicated or not tolerated) for continuous glycemic and metabolic advantages. **(A)**
- To reduce the risk of hypoglycemia and treatment burden upon beginning insulin therapy in individuals with type 2 diabetes, reconsider the need for and/or dose of glucose-lowering medications with a higher risk of hypoglycemia (sulfonylureas and meglitinides). **(A)**

Illustration (4) Management Options for Type 2 Diabetes ***(ElSayed et al., 2023j; Samson et al., 2023)***

Management approach

Healthy lifestyle behaviors; diabetes self-management education and support (DSMES); social determinants of health (SDOH)

To avoid therapy inertia, regular monitoring and change should occur every 3-6 months

Patient with risk factors

Patient without risk factors

The treatment goal is to reduce cardiorenal risk + control blood sugar levels. *

The treatment goal is weight management + controlling blood sugar levels. **(A)**

Patients with ASCVD or with high risk **

Patients with HF (HFrEF or HFpEF)

Patients with CKD**** on max. dose of ACEI/ARB

- Consider a regimen with high to very high dual glucose and weight efficacy in obese patients.
- Consider monotherapy or combination medication to meet glycemic targets while avoiding hypoglycemia

GLP-1RA ***or*** SGLT2i with proven CVD benefit ***

SGLT2i with proven HF benefit ***

Preferably SGLT2i *****or*** GLP-1RA if SGLT2i not tolerated or contra-indicated

If A1C above target

If A1C above target

- If patient on GLP-1RA, consider adding SGLT2i or vice versa.
- low dose TZD

- If patient on SGLT2i, consider incorporating GLP-1RA or vice versa.

Medications' efficacy in <u>decreasing blood glucose</u>

Very high: certain GLP-1RA "dulaglutide high dose, semaglutide", insulin, combination oral, combination injectable "lixisenatide/insulin"

High: certain GLP-1RA "exenatide-ER, liraglutide", metformin, SGLT2i, SU, TZD.

Intermediate: DPP-4i

Medications' efficacy on <u>weight loss</u>

Very high: GLP-1RA "semaglutide"

High: GLP-1RA "dulaglutide, liraglutide"

Intermediate: GLP-1RA" exenatide-ER", SGLT2i

Neutral: DPP-4i, metformin

If more cardio-renal risk reduction or glycemic control is required, or if A1C is over target

Determine obstacles to goals:

Consider referring to DSMES to increase self-efficacy in achieving goals.
Consider using technology (e.g. diagnostic CGM) to determine therapeutic gaps and tailor treatment.
Determine and address SDOH and medication interactions that influence achievement of goals.

If all barriers are removed, the patient is already on GLP-1 RA or if this is not appropriate and A1C remains above the target OR insulin is preferred "if a diagnosis of type 1 diabetes is a possibility, evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10%) or BG levels (≥300 mg/dl)"

Add basal insulin

For people on GLP-1 RA and basal insulin combination, use of a fixed-ratio combination product (iDegLira or iGlarLixi)

Basal insulin should be chosen based on individual factors such as cost.
Physicians may consider prescribing glucagon in the event of an emergency hypoglycemia.

Add morning dose of long acting basal analog or bedtime NPH insulin "if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with a morning dose of a long-acting basal insulin,consider switching from evening NPH to a basal analog."
Initiation: Start 10 units per day **OR** 0.1–0.2 units/kg per day
Titration:

- Set FPG target
- Select an evidence-based titration protocol, such as increasing 2 units every 3 days to achieve the FPG target without hypoglycemia
- Determine the cause of hypoglycemia; if no apparent explanation is found, reduce the dose by 10-20%

Assess adequacy of basal insulin dose

- ***If the patient is on bedtime NPH, consider switching to a twice-daily NPH regimen. One possible strategy is as follows:***

Initiation:

- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

Titration:

- Titrate according to individualized needs

- ***Consider clinical and laboratory signals to assess overbasalization* and the necessity for additional therapy.***

- If A1C above target and not already on GLP-1 RA, GLP-1 RA should be added before starting prandial insulin.

* Overbasalization: A basal dose > ~0.5 units/kg/day, hypoglycemia (aware or unaware), large bedtime -morning glucose or or postprandial- to-preprandial glucose differential (e.g., bedtime–morning glucose differential ≥ 50 mg/dL), and excessive glycemic variability.

If A1C above target

Add prandial insulin

"If adding prandial insulin to NPH, consider starting a self-mixed or premixed insulin regimen to reduce the number of injections."

Usually one dose with the largest meal or meal with the highest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate.

Initiation

- 4 units per day or 10% of basal insulin dose
- If A1C <8% consider lowering the daily basal dose by 4 units or 10% of basal dose

Titration: depend on A1C or home glucose monitoring.

- Increase dose by 1–2 units or 10–15% twice weekly
- For hypoglycemia determine cause, if no apparent explanation is found, reduce the relevant dose by 10-20%

If A1C above target

Additional prandial insulin injections are given in stepwise approach (i.e., two, then three injections)

Proceed to the entire basal-bolus regimen "basal and prandial insulin with each meal "

Provide greater flexibility for people who eat on irregular schedules.

Consider self-mixed/split insulin regimen

Can adjust NPH and short/rapid-acting insulins separately

Initiation:

- Total NPH dose = 80% of current NPH dose
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 units of short/rapid-acting insulin to each injection or 10% of reduced NPH dose

Titration:

- Titrate each regimen component depended on individualized needs

Consider twice-daily premixed insulin regimen

(e.g. NPH/regular 70/30, Aspart 70/30)

Initiation:

Usually unit per unit at the same total insulin dose, but this may need to be adjusted depended on individual needs.

Titration:

Titrate depended on individualized needs.

Is a simple, convenient methods of distributing insulin throughout the day, less expensive

Individuals with suboptimal blood glucose control, particularly those requiring large insulin doses, may benefit from adjunctive use of a thiazolidinedione or an SGLT2 inhibitor if they are not already taking them to improve control and reduce the amount of insulin required, though potential side effects should be considered.

Illustration (5) Management Approach for Type 2 Diabetes Management adapted from *(ElSayed et al., 2023j)*

*In people with chronic kidney disease (CKD); heart failure (HF); established cardiovascular disease (CVD) or multiple risk factors for CVD, the decision to use GLP-1RA or SGLT2i with proven benefit should be independent of background use of metformin.

** ASCVD includes established CVD "myocardial infarction (MI), stroke, and any revascularization procedures"; transient ischemic attack; unstable angina; amputation; and symptomatic or asymptomatic coronary artery disease, multiple risk factors for CVD "age ≥55 years with two or more additional risk factors such as hypertension, obesity, dyslipidemia, smoking, or albuminuria". A strong recommendation is warranted for people with established CVD; while a weak recommendation is for those with indicators of high cardiovascular (CV) risk. ASCVD calculator https://www.mdcalc.com/calc/3398/ascvd-atherosclerotic-cardiovascular-disease-2013-risk-calculator-aha-acc

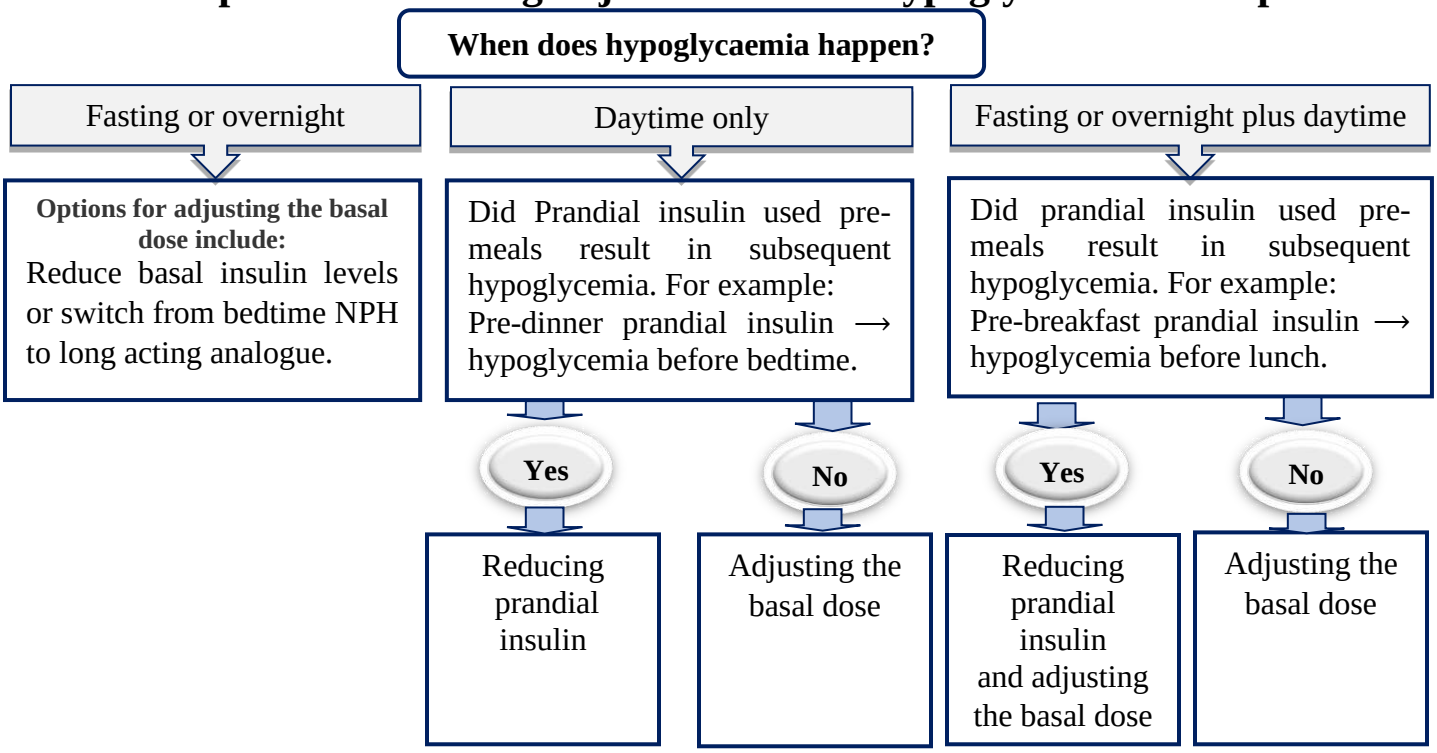
*** For GLP-1 RA benefits are reducing major adverse cardiovascular events (MACE), CV death, all-cause mortality, MI, stroke, and renal endpoints. For SGLTi benefits are reducing the risk of MACE, CV death, all-cause mortality, MI, hospitalization for heart failure (HHF), and renal outcomes.
**** CKD: estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2 or albuminuria "albumin to creatinine ratio (ACR) ≥ 30 mg/g". These measurements may vary over time; thus, a repeated measure is required to document CKD.
***** Use SGLT2i in people with an e-GFR ≥ 20 ml/min/1.73 m2; Once started, it should be maintained until dialysis or transplantation begins.

ASCVD, atherosclerotic cardiovascular disease; **ACEi**, angiotensin-converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **DPP-4i**, dipeptidyl peptidase 4 inhibitor; **GLP-1 RA**, glucagon-like peptide 1 receptor agonist; **HFpEF**, heart failure with preserved ejection fraction; **HFrEF**, heart failure with reduced ejection fraction; **SGLT2i**, sodium-glucose cotransporter 2 inhibitor; **TZD**, thiazolidinedione; **SU**, sulfonylurea.

Important notes on management approach *(ElSayed et al., 2023j)*

- Independent of A1C and in consideration of individual-specific factors, SGLT2i with proven benefit (empagliflozin, canagliflozin, dapagliflozin) and/or GLP-1 RA with demonstrated cardiovascular disease benefit (liraglutide, semaglutide, and dulaglutide) is recommended as part of the glucose management strategy and comprehensive cardiovascular risk reduction in individuals with T2DM who have established ASCVD or indicators of high cardiovascular risk, established kidney disease, or heart failure. **(A)**
- Human insulin (NPH and regular) may be the appropriate choice of therapy for many people with type 2 diabetes (e.g., those with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns), and clinicians should be familiar with its use.
- Individuals with type 2 diabetes are more insulin resistant than individuals with type 1 diabetes, require greater daily doses (1 unit/kg), and have a lower incidence of hypoglycemia.
- With significant additions to the prandial insulin dose, especially with the evening meal, consideration should be given to lowering basal insulin.
- There are two different once-daily, fixed dual combination drugs containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide (iGlarLixi) and insulin degludec plus liraglutide (iDegLira).
- When compared to intensified insulin regimens, the combination of basal insulin with GLP-1 RA offers potent glucose-lowering effects as well as less weight gain and hypoglycemia.
- When starting combination injectable therapy or intensification of insulin therapy, metformin, SGLTi should be continued while sulfonylureas and DPP-4 inhibitors are routinely tapered or terminated.
- Once a basal-bolus insulin regimen is started, dose titration is important, with modifications made in both mealtime and basal insulins depending on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation.

Proper insulin dosing adjustment when hypoglycemia develops



Options for adjusting the basal dose include:

- Decreasing the basal insulin dose by 4 units or 10% (whichever is higher).
- For patients who take NPH, converting to detemir, glargine, or degludec at 80 to 90% of the current total daily NPH dose.
  - However, for individuals with frequent and/or severe hypoglycemia, it is advised to decrease the dose significantly (e.g., by 20 to 50%) and repeat the basal insulin titration.

Options for reducing prandial insulin

- ***If a lifestyle factor is found to be the cause of the hypoglycemia***, insulin should be adjusted to account for the change in lifestyle. Furthermore, patients should be queried about the timing of their prandial insulin dose and optimal timing should be reinforced if it appears to be contributing to episodes of hypoglycemia (for example, if the insulin is taken after a meal rather than before the meal).
- ***If the hypoglycemia is not severe***, a standard method is to reduce the dose based on how much prandial insulin the patient is taking at the relevant mealtime:
- ≤10 units: Reduce by 2 units
- 11 to 20 units: Reduce by 4 units
- >20 units: Reduce by 6 to 10 units or 50%
- ***If the hypoglycemia is severe or serious,*** it is advisable to decrease the dose significantly (by 20 to 50%) and repeat the titration, or to stop the prandial insulin and reinitiate/retitrate if necessary.

Illustration (6) Insulin Dosing Adjustment during Hypoglycaemia ***(ElSayed et al., 2023j; Wexler et al., 2024a)***

Diabetes Care in the Hospital

- If an A1C test has not been performed in the previous three months, it should be performed on all persons admitted to the hospital with diabetes or hyperglycemia "blood glucose >140 mg/dL" ***(ElSayed et al., 2023i).*** **(B)**
- If the A1C value ≥ 6.5% upon admission, it indicates that diabetes began before hospitalization ***(ElSayed et al., 2023i).***
- Institutions should implement protocols using validated written or computerized provider order entry sets for managing dysglycemia in all departments of the hospital (such as emergency department, intensive care unit [ICU] and non-ICU wards, dialysis units, behavioral health units, and gynecology-obstetrics/delivery units) that allow for a personalized approach, including glucose monitoring, insulin and/or noninsulin therapy, hypoglycemia management, diabetes self-management education, nutrition recommendations, and transitions of care ***(ElSayed et al., 2023i).*** **(B)**
- Glucose monitoring should be undertaken before meals in diabetic hospitalized patients who are eating; glucose monitoring is recommended every 4-6 hours in those who are not eating. For the safe administration of intravenous insulin, blood glucose monitoring is necessarily performed every 30 minutes to every 2 hours ***(ElSayed et al., 2023i).***
- People with diabetes who use a personal continuous glucose monitoring (CGM) device should continue to use it during hospitalization if clinically appropriate, with confirmatory point-of-care (POC) glucose measurements for insulin dosing decisions and hypoglycemia assessment, if resources and training are available, and according to an institutional protocol ***(ElSayed et al., 2023i).*** **(B)**

Non-critically care settings ***(ElSayed et al., 2023i)***

- For **non-critically** ill hospitalized patients **with inadequate oral intake or who are taking nothing by mouth**, basal insulin or a basal plus bolus correction insulin regimen is the optimal treatment. **(A)**
- For the majority of **non-critically** ill hospitalized patients **with appropriate nutritional intake**, an insulin regimen including basal, prandial, and correction components is the chosen treatment. **(A)** However, in certain cases, continuing home therapy, such as oral glucose-lowering medicines such as DPP-4i, may be beneficial.
- It is recommended that persons with type 2 diabetes who are hospitalized with heart failure start or continue taking a sodium-glucose cotransporter 2 inhibitor throughout hospitalization and after discharge, if there are no contraindications, and after recovering from the acute illness. **(A)**
- If oral drugs are held in the hospital but will be resumed after discharge, there should be a protocol in place to guide the resumption of home medications 1-2 days before discharge.
- **In the inpatient setting,** the use of corrective or supplementary insulin without basal insulin (also known as a sliding scale) is discouraged except for persons in noncritical care with type 2 diabetes who have mild hyperglycemia. **(A)**
- Several reports have found that inpatient use of insulin pens is safe and may be related to higher nurse satisfaction when compared to the use of insulin vials and syringes with safety controls in place provided that using a pen for each patient. **(under full supervision of nurses during administration).**
- Insulin combinations, such as 70/30 insulins, are not generally advised for in-hospital use since they are associated with greater hypoglycemia.

Critical care settings ***(ElSayed et al., 2023i)***

- In the **critical care** situation, continuous intravenous insulin infusion is the most effective approach for reaching glycemic goals. Intravenous insulin infusions should be given under approved written or computerized protocols that allow for predetermined modifications in the infusion rate while accounting for glycemic variations and insulin doses.

- When a blood glucose value of < 70 mg/dL is recorded, treatment regimens should be reviewed and altered as needed to prevent additional hypoglycemia. **(C)**
- A person with type 1 or type 2 diabetes who is transitioning to a subcutaneous regimen should receive a dose of subcutaneous basal insulin 2 hours before discontinuing the intravenous infusion. Before stopping an insulin infusion, starting subcutaneous basal insulin may assist in reducing rebound hyperglycemia.
- The basal insulin dose is best determined based on the insulin infusion rate over the last 6-8 hours when stable glycemic goals were met.
- According to emerging data from several studies, administering a low dose (0.15-0.3 units/kg) of basal insulin analog in addition to intravenous insulin infusion may reduce insulin infusion duration and length of hospital stay, as well as prevent rebound hyperglycemia without increasing the risk of hypoglycemia.

Standards for Special Situations

Older Diabetic Patients' Considerations in Management

- Diabetes overtreatment is widespread in the elderly and should be avoided ***(ElSayed et al., 2023g).*** **(B)**
- When creating treatment plans, consider the costs of care and insurance coverage rules to lessen the potential of cost-related barriers to adherence and self-management ***(ElSayed et al., 2023g).*** **(B)**

Considerations for oral agents use in older patients ***(ElSayed et al., 2023g)***

- Medication with a reduced risk of hypoglycemia is favored for older persons with type 2 diabetes, particularly those with hypoglycemia risk factors using personalized glycemic targets. **(B)**

- **Metformin** is the first-line treatment for older persons with type 2 diabetes unless contraindicated.
- **Thiazolidinediones (TZD):** should be used with extreme caution in insulin-treated older persons, as well as those with or at risk of heart failure, osteoporosis, falls or fractures, and/or macular edema. Using of lower dosages in combination with other drugs may alleviate these adverse effects.
- **Insulin secretagogues (ulfonylureas (SU) and others):** are related to hypoglycemia and should be used with caution.
  - If used, SUs with a shorter duration of action, such as glipizide, are recommended.
  - Glyburide is a longer-acting sulfonylurea that should be avoided in elderly patients.
- **Incretin-Based Therapy (dipeptidyl peptidase 4 (DPP-4) inhibitor)**
  - DPP-4 inhibitors offer few side effects and a low risk of hypoglycemia, but their cost may be a barrier for certain elderly patients.
  - DPP-4 inhibitors do neither improve nor worsen severe unfavorable cardiovascular events.
- **Sodium glucose cotransporter2 (SGLT2i)** is taken orally, which may be more convenient for diabetic elderly people. Although these medicines have demonstrated cardiovascular and renal advantages, adverse effects such as volume depletion, urinary tract infections, and increasing urine incontinence may be more likely in the elderly.

Considerations for injectable agents use in older patients ***(ElSayed et al., 2023g)***

- Injectable agents include GLP-1 RA and insulin.

Use of GLP-1 RAs

- GLP-1 RAs have been shown to offer cardiovascular advantages in diabetics. Except for oral semaglutide, these medications are injectables that require visual, motor, and cognitive skills to administer properly.
- Agents with a weekly dose schedule may lessen the administrative burden.
- GLP-1 receptor agonists can also cause nausea, vomiting, and diarrhea.
- GLP-1 receptor agonists may not be favored in elderly patients having unexplained weight loss due to the gastrointestinal adverse effects of this class.

Use of insulin

- Simplification of complex treatment plans (particularly insulin) is recommended to lower the risk of hypoglycemia and polypharmacy, as well as the treatment load, if achievable utilizing tailored glycemic targets. **(B)**

Simplification of Complex Insulin Therapy in Older Adults with Type 2 Diabetes

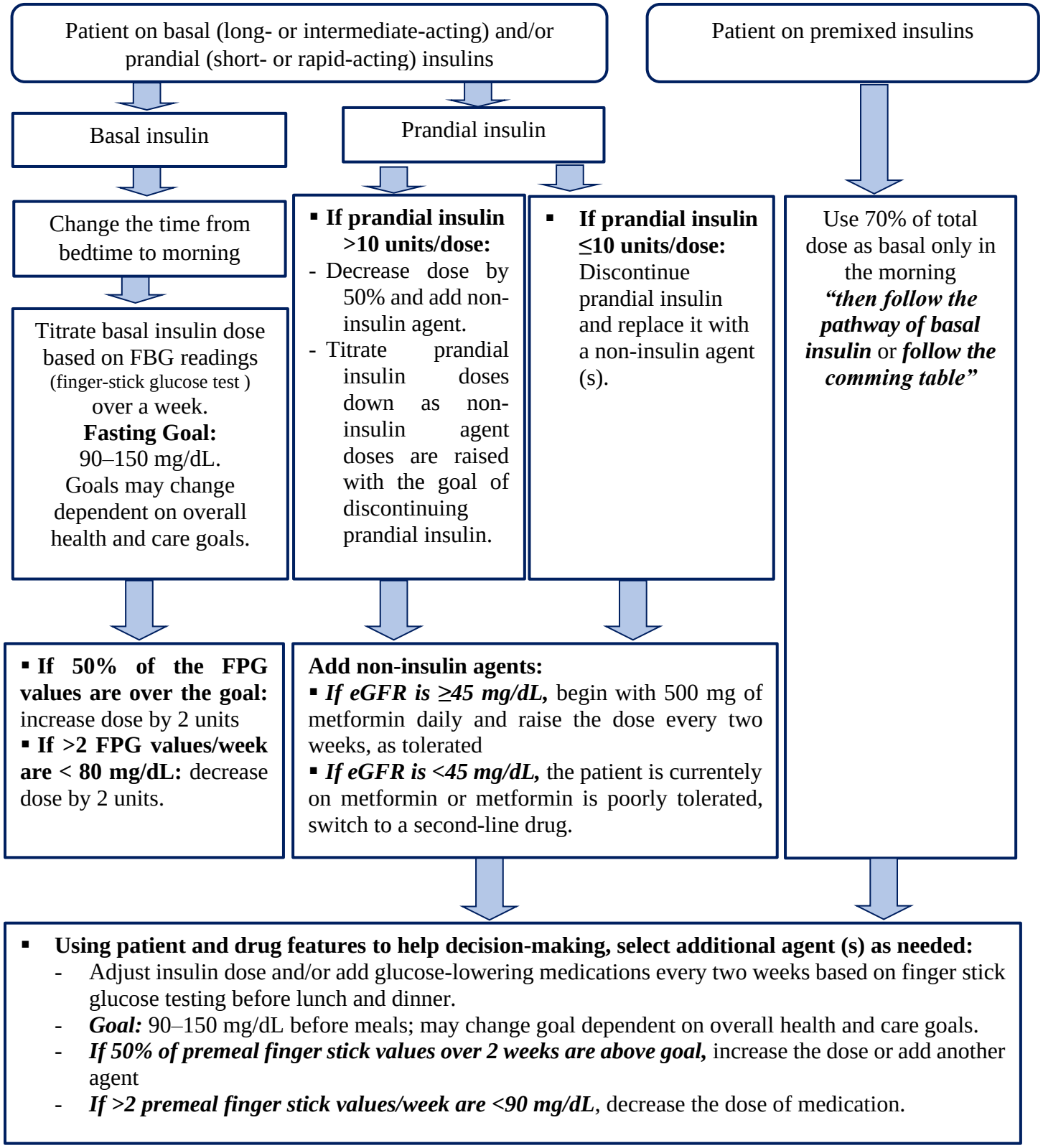


Illustration (7) Simplification of Complex Insulin Therapy in Older Adults with Type 2 Diabetes adapted from *(ElSayed et al., 2023g)*

Additional/Important Tips

The patient should be counselled about:

- At bedtime, avoid using rapid or short-acting insulin.
- While adjusting prandial insulin, a simplified sliding scale, for example, may be used:
  - ***Premeal glucose >250 mg/dL,*** give 2 units of short- or rapid-acting insulin.
  - ***Premeal glucose >350 mg/dL,*** give 4 units of short- or rapid-acting insulin.
- Stop using the sliding scale when it is not required daily.
- Insulin therapy**:** To use insulin therapy, patients or their carers must have adequate visual, motor, and cognitive abilities. In older patients, once-daily basal insulin has been associated with few adverse effects. As previously said, the treatment should be simplified.

Enteral/Parenteral Nutrition

- Individuals receiving enteral or parenteral nutrition who require insulin should have insulin orders that address their basal, prandial, and correctional needs. Even if feedings are stopped, persons with type 1 diabetes must continue to receive basal insulin ***(ElSayed et al., 2023i).***
- Most persons using basal insulin should maintain their basal dose, whereas the insulin dose for the total daily nutritional component in enteral and parenteral formulae can be estimated as 1 unit of insulin for every 10-15 g carbohydrate ***(ElSayed et al., 2023i).***
- Giving NPH insulin twice or three times daily (every 8 or 12 hours) to meet individual needs is a reasonable option. Insulin doses should be adjusted regularly. Correctional insulin should be given subcutaneously every 6 h with human regular insulin. If enteral nutrition is stopped, a dextrose infusion should be begun quickly to prevent hypoglycemia and to give time to choose more appropriate insulin dosages ***(ElSayed et al., 2023i).***
- Adults receiving enteral bolus feedings should have 1 unit of regular human insulin or rapid-acting insulin per every 10-15 g of carbohydrate subcutaneously administered before each feeding. Before each feeding, corrective insulin coverage should be added as needed to alleviate any hyperglycaemia ***(ElSayed et al., 2023i).***
- In persons undergoing nocturnal tube feeding, NPH insulin delivered at the start of the feeding is an acceptable way to cover this nutritional load ***(ElSayed et al., 2023i).***
- Human regular insulin may be added to the solution for persons receiving continuous peripheral or central parenteral feeding, especially if >20 units of corrective insulin have been necessary in the previous 24 hours. A beginning dose of 1 unit of human regular insulin for every 10 g of dextrose has been advised, and the solution should be adjusted daily. If parenteral nutrition is discontinued or held, adding insulin to the parenteral nutrition bag is the safest strategy to prevent hypoglycemia. To treat hyperglycemia, corrective insulin should be given subcutaneously ***(ElSayed et al., 2023i).***
- Because continuous enteral or parenteral nourishment results in a continuous postprandial state, efforts to reduce blood glucose levels to less than 140 mg/dL raise the risk of hypoglycemia in these patients significantly ***(ElSayed et al., 2023i).***

Hospitalized Patients Receiving Glucocorticoid Therapy

- Administering intermediate-acting (NPH) insulin to people on once- or twice-daily steroids is a standard strategy. NPH is typically given in addition to daily basal-bolus insulin or oral glucose-lowering drugs. Because NPH action peaks after 4-6 hours after treatment, it is best to be administered concomitantly with intermediate-acting steroids (e.g., prednisone) ***(ElSayed et al., 2023i).***
- Long-acting glucocorticoids such as dexamethasone, as well as multidose or continuous glucocorticoid therapy, may need the administration of long-acting basal insulin to control fasting blood glucose levels ***(ElSayed et al., 2023i).***
- In addition to basal insulin, greater doses of prandial (if eating) and corrective insulin, often as much as 40-60% or more, are often required for higher glucocorticoid dosages ***(ElSayed et al., 2023i).***

- Whatever insulin orders are initiated, daily adjustments depending on glycemia levels and anticipated changes in glucocorticoid type, dose, and duration, as well as blood glucose monitoring, are crucial to minimizing rates of hypoglycemia and hyperglycemia ***(ElSayed et al., 2023i).***

Perioperative Care

The following strategies could be considered ***(ElSayed et al., 2023i)***

1) People with diabetes who are at high risk of ischemic heart disease, as well as those with autonomic neuropathy or renal failure, should have a preoperative risk assessment.
2) When possible, the A1C goal for elective surgeries should be <8%.
3) Within 4 hours of operation, the target range for BG in the perioperative period should be 100-180 mg/dL. CGM should not be used alone for glucose monitoring during surgery.
4) On the day of the operation, metformin should be held.
5) SGLT2 inhibitors must be stopped three or four days in the case of Ertugliflozin before the operation.
6) Other glucose-lowering medicines should be held the morning of the operation or procedure, and half of the NPH dose or 75-80% of long-acting analog doses should be administered, depending on the type of diabetes and clinical judgment.
7) In comparison to standard dose, a 25% reduction in basal insulin administered the evening before surgery is more likely to fulfill perioperative blood glucose targets while lowering the risk of hypoglycemia.
8) Monitor blood glucose levels at least every 2–4 hours when the patient is not taking anything by mouth and dose with short or rapid-acting insulin as required.
9) GLP-1RA: Limited data is available. Holding GLP-1 agonists daily dose on the day of surgery or weekly dose of GLP-1 agonists before elective surgery due to the presence of some case reports of aspiration ***(ElSayed et al., 2023; Joshi et al., 2023).***
10) Perioperative glycemic goals tighter than 80-180 mg/dL did not enhance outcomes and were linked with greater hypoglycemia.
11) Basal insulin plus premeal short- or rapid-acting insulin (basal-bolus) coverage has been associated with better glycemic outcomes and lower rates of perioperative complications in non-cardiac general surgery patients when compared to reactive, correction-only short- or rapid-acting insulin coverage alone with no basal insulin dosing.

Non-Pharmacological Treatment of Diabetes Mellitus

- Optimal diabetes mellitus management includes both pharmacological and non-pharmacological measures ***(Raveendran, 2018).***
- Non-pharmacological measures include proper education to diabetic patients about healthy lifestyle changes as dietary interventions, as lifestyle modifications are very important tools for lowering the progression of hyperglycemia, attention to cardiovascular risk and associated comorbidities, and improving overall physical and mental health ***(Blum et al., 2021; CDC, 2022; Raveendran, 2018).***
- Non-pharmacological measures include education about:
    1. Medical Nutrition Therapy (MNT)
    2. Smoking cessation

1. Medical Nutrition Therapy (MNT)

It is the process through which nutrition prescriptions are tailored to each individual based on medical, lifestyle, and personal considerations ***(Delahanty et al., 2023).***

Individualized MNT should be provided for all diabetic people ***(Raveendran, 2018).***

MNT general goals ***(Delahanty et al., 2023; Delahanty et al., 2024; Raveendran, 2018)***

- To improve overall health by eating healthy foods.
- Is considered a secondary, or tertiary preventive measure:
    - Secondary preventive measure: By reducing/preventing diabetic consequences such as hypoglycemia and ketoacidosis and micro/macrovascular problems, and hence achieving tight glycemic control through food modification.
    - Tertiary preventative measure: Controlling diabetes-related complications such as cardiovascular disease or kidney disease.

MNT implementation benefits ***(Delahanty et al., 2023; Delahanty et al., 2024; Raveendran, 2018)***

- Maintain as close to normal blood glucose levels as possible, as well as a significant reduction in A1C levels, by incorporating insulin therapy or medication into each individual's diet and physical activity habits.
- Optimize blood pressure and lipid levels.
- Provide enough calories to achieve and maintain healthy body weight, as well as proper growth and development.
- Manage other concomitant illnesses such as hypertension, hyperlipidemia, renal, cardiovascular, and celiac disease.

MNT components in T1DM ***(Delahanty et al., 2023)***

- Personal dietary preferences
- Consistency in daily carbohydrate intake
- Adjusting insulin dose according to variations in diet, blood glucose, and physical activity
- Meal-insulin timing
- Weight management
- Nutritional content (balance of selected protein, quality carbohydrates, and fats)

MNT components in T2DM ***(Delahanty et al., 2024)***

- Consistency in daily carbohydrate intake at meals and snacks
- Timing of meals and snacks
- Physical activity
- Weight management and caloric intake (balanced with caloric expenditure)

- Nutritional content

- Accordingly, the principles of MNT of T1DM are similar for the management of T2DM, but there is an important issue that should be considered which is insulin dose calculation and modification according to blood glucose, diet nature, and physical activity in patients managed with insulin.

MNT components

1.1 Personal dietary preferences: During the implementation of MNT, individual dietary preferences should be considered to ensure proper commitment ***(Delahanty et al., 2023).***

1.2 Consistency in daily carbohydrate intake

- Variations in food intake, particularly carbohydrate intake, can cause irregular blood glucose levels and hypoglycemia in diabetic patients, especially those on insulin, sulfonylureas, or other secretagogues. Intensive insulin regimens that combine basal insulin with boluses or injections of rapid-acting pre-meal insulins allow for some meal carbohydrate flexibility ***(Delahanty et al., 2023; Delahanty et al., 2024).***
- There are numerous meal-planning ways to attain carbohydrate consistency, including basic and advanced carbohydrate counting, the exchange system, and sample menus. An individual's optimal strategy is chosen by an assessment of their lifestyle and learning skills ***(Delahanty et al., 2023).***
  - ***Basic carbohydrate counting:*** The purpose of basic carbohydrate counting is to assist glycemic control by maintaining a consistent pattern of carbohydrate consumption with meals and snacks from day to day ***(Delahanty et al., 2023; Delahanty et al., 2024).***
  - ***Advanced carbohydrate counting "calculation of Insulin/Carbohydrate Ratio (ICR)":*** As discussed before in outpatient settings section ***(Delahanty et al., 2023).***
  - ***The exchange system:*** To ease the teaching of carbohydrate consistency ideas, the food groups have recently been divided into three categories. These three categories are carbohydrates, protein (meat/meat) alternatives, and fat. Each item in a group was "exchangeable" because it had roughly the same nutritional value in terms of calories, carbohydrates, protein, and fat. The exchange lists flag foods that are rich in sodium and high in fiber to alert readers to foods high in sodium and good sources of fiber ***(Delahanty et al., 2023; Delahanty et al., 2024; Wheeler et al., 2008).***
  - ***Sample menus (meal menus):*** Menus are developed after an assessment of a person's typical food consumption; they are best suited for persons who have fairly routine eating habits and who do not eat a large variety of foods. Menus also are helpful for persons who require systematic instruction on what to eat ***(Delahanty et al., 2023).***

1.3 Adjusting insulin dose according to variations in diet, blood glucose, and physical activity

- An important component of MNT in patients on insulin therapy is a modification of insulin doses according to several parameters such as diet components (carbohydrate, fat, and protein), blood glucose level, and physical activity of the patient to ensure glycaemic control. So, the following parameters should be considered:
  - ***Adjustments for carbohydrate meals:*** Insulin doses should be adjusted by calculating ICR as mentioned before "a main physician's role" ***(Delahanty et al., 2023).***
  - ***Adjustments for high-fat or protein meals:*** Estimating insulin doses based solely on the carbohydrate content of the meal will be insufficient for many people with type 1 diabetes who consume a lot of fat and protein. Glycemic excursions and insulin dosage can be dramatically influenced by the amount of dietary fat and protein in a meal. So, it should be considered during dosing calculation ***(Delahanty et al., 2023).***
  - ***Adjustments for elevated blood glucose (Insulin sensitivity factor "ISF" calculation):*** As discussed before in the outpatient settings section ***(Delahanty et al., 2023).***
  - ***Adjustments for physical activity:*** Consider the timing of exercise concerning insulin dose, type, route of delivery, and injection time according to specialists' evaluation ***(Delahanty et al., 2023).***

1.4 Meal-insulin / insulin secretagogues timing *(Delahanty et al., 2023; Delahanty et al., 2024)*

- Meal timing at regular intervals (consistency in meal timing/fixed time) is critical for achieving glycemic targets and avoiding hypoglycemia in persons receiving fixed doses of short- and intermediate-acting insulins or basal plus oral drugs or insulin secretagogues. While basal-bolus insulin regimens provide greater meal time flexibility.
- An alternative method to a fixed mealtime and carbohydrate consumption is to counsel the patients about the physician's instructions for calculating how much short- or rapid-acting insulin is required to cover a specific amount of carbohydrate (ICR). However, it is important to notice that ICR can vary depending on several factors and that individuals may require a different ICR at different meals.
- Despite the ICR drawbacks, once the ratio is determined, patients with type 1 diabetes can change the amount of carbohydrates consumed at each meal.
- It is critical to assess persons with T1DM, particularly young women, for an eating disorder as well as insulin omission for weight reduction, and to provide appropriate psychological and nutritional counseling and support as needed.

1.5 Physical activity

- **Evaluation and assessment:** According to the healthcare provider assessment, further investigations will be ordered or not ***(Riddell et al., 2024).***
- **Type and frequency of exercise:** It should be determined according to the assessment of the specialists. All individuals should prevent extended sitting/sedentary behavior by standing, walking, or doing other activities every 30 minutes ***(Blum et al., 2021; ElSayed et al., 2023c; Raveendran, 2018).***

Benefits

- Improves blood sugar levels by enhancing both non-insulin-mediated and insulin-mediated glucose uptake ***(Delahanty et al., 2023; Delahanty et al., 2024; Raveendran, 2018; Riddell et al., 2024).***
- Improves glycemic indices "especially in type 2 diabetes" ***(Riddell et al., 2024).***
- Increases glucose disposal (mitochondrial oxidation and storage as muscle glycogen) and improves muscle mass and morphology ***(Riddell et al., 2024).***
- Improves whole-body insulin sensitivity and enhances insulin sensitivity for up to 48 hours after physical activity ***(Blum et al., 2021; ElSayed et al., 2023c; Delahanty et al., 2024; Raveendran, 2018; Riddell et al., 2024).***
- Improves cardiovascular health and other cardiovascular risk factors "for example, dyslipidemia and hypertension" ***(Delahanty et al., 2023; Delahanty et al., 2024; Raveendran, 2018; Riddell et al., 2024).***
- Aids in weight loss and maintenance ***(Delahanty et al., 2023; Delahanty et al., 2024; Riddell et al., 2024).***
- Reduces central obesity in young people ***(Blum et al., 2021; ElSayed et al., 2023c).***
- Improve physical fitness, overall well-being, mood, and quality of life ***(Delahanty et al., 2023; Delahanty et al., 2024; Raveendran, 2018).***

Glycemic management during exercise

<u>For patients taking insulin or insulin secretagogues</u>

- Exercise raises the risk of hypoglycemia ***(Raveendran, 2018).***
- The risk of hypoglycemia is also affected by the duration and intensity of exercise, as well as the time of day exercise is performed in relation to the last food consumed ***(Raveendran, 2018).***
- Increasing insulin sensitivity through exercise and replenishing depleted glycogen stores can result in delayed hypoglycemia several hours after the exercise termination "e.g., four to eight hours after the exercise" ***(Raveendran, 2018; Riddell et al., 2024).***
- Adjustments to insulin or insulin secretagogues (sulfonylureas, glinides) before, during, and after exercise are often empiric and aided by glucose monitoring (with fingersticks every 30 to 45 minutes, or using a continuous glucose monitor [CGM]) for patients who take insulin or insulin secretagogues (sulfonylureas, glinides). Blood glucose levels can be measured, documented, and predicted for future exercise sessions ***(Raveendran, 2018; Riddell et al., 2024).***

- If the pre-exercise blood glucose level is <100 mg/day, insulin- or insulin secretagogue-treated patients should take additional food, in the form of 15 to 30 grams of quickly absorbed carbohydrate (such as glucose tablets, hard candies, or juice), which should be given 15 to 30 minutes before exercise and approximately every 30 minutes during exercise, based on repeat blood glucose testing during the exercise ***(Raveendran, 2018; Riddell et al., 2024).***

Type 2 diabetes not taking insulin or insulin secretagogues

- Hypoglycemia is uncommon in people with T2DM who are not taking insulin or insulin secretagogues, therefore glucose monitoring during exercise, increased carbohydrate consumption, and medication modifications are usually less important ***(Riddell et al., 2024).***

1.6 Weight management

- Overweight due to physical inactivity and over-nutrition, or any other reason, results in fat buildup mostly in the abdomen and visceral regions. This adiposity modulates several hormonal and chemical mediators in the body, resulting in "diabesity", the term coined to connect diabetes and obesity and increase insulin resistance and impaired-cell function (decreased insulin secretion, lipotoxicity), resulting in the development of T2DM and deterioration of T1DM ***(Delahanty et al., 2023; Raveendran, 2018).***

Benefits

- Useful in the control, and remission of type 2 diabetes ***(Evert et al., 2019; Raveendran, 2018).*** Diabetes remission is defined by an international group of experts convened by the American Diabetes Association (ADA) as "an A1C less than 6.5 % maintained for at least three months after discontinuation of any glucose-lowering medications" ***(Wexler et al., 2024b).***
- Improve cardiometabolic health and reduce incidence and severity of microvascular diabetes complications such as stroke, retinopathy, and nephropathy in patients with T1DM and T2DM ***(Evert et al., 2019; Delahanty et al., 2024).***
- Improves insulin sensitivity by decreasing insulin resistance ***(Evert et al., 2019; Raveendran, 2018).***

Weight loss strategies: They include physical activity, diet modification, and medication use, and may require bariatric surgery. The choice of the suitable strategy is based on specialists' evaluation, and assessment ***(Delahanty et al., 2024).***

1.7 Nutritional content

- For individuals with diabetes, the appropriate macronutrient composition of the diet should be customized based on weight loss objectives, other metabolic requirements (e.g., hypertension, dyslipidemia, nephropathy), and dietary preferences ***(Aas et al., 2023; Blum et al., 2021; ElSayed et al., 2023c; Delahanty et al., 2024).***
- There is no ideal percentage of calories from carbohydrates, protein, and fat for all diabetic individuals ***(ElSayed et al., 2023c; Delahanty et al., 2024).***
- There are several suitable eating patterns such as low fat, low carbohydrate, Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and vegetarian ***(Aas et al., 2023; Delahanty et al., 2024; ElSayed et al., 2023c; Evert et al., 2019).***
- The choice of suitable nutritional content is based on the specialists' assessment.

2. Smoking Cessation

All people should be educated and supported for smoking cessation importance as discussed in the outpatient settings section.

Pharmacological Treatment of Diabetes Mellitus

(A) Injectable agents

I. Insulin hormone

- The release of normal body insulin occurs in two phases ***(Omar-Hmeadi & Idevall-Hagren, 2020):***
  - **1st phase:** "Spike in plasma insulin levels" a sharp and rapid rise in plasma insulin concentrations responded to the rise in plasma glucose levels. This phase lasts for a few minutes *(prandial).*
  - **2nd phase:** A slow and sustained release of insulin *(basal).*

Insulin Preparations Registered in Egypt

1) **Monophasic Insulin Preparations:** Monophasic insulin products mimic only one of the two phases of insulin release in the human body "1st ***or*** 2nd phase" and are subdivided based on their pharmacokinetic profiles:

a) Short and Rapid-Acting Preparations

- Short and rapid-acting insulins ***mimic 1st phase*** after meals. Short and rapid-acting insulin preparations, unlike other categories, can be used intravenously to control diabetic ketoacidosis in hospitals; and can be given in insulin pumps.
- Rapid-acting insulin analogs include lispro, aspart, and glulisine. Short-acting insulin includes regular insulin.

b) Intermediate-Acting Preparations

- Intermediate-acting insulins, also known as NPH or isophane insulins ***mimic 2nd phase***. They are variants of either regular insulin or its rapid-acting analogs, where they are suspended by complexation with protamine; this slows down their absorption from the injection site, and hence delays the onset and peak of their action and extends the duration of their effect.

c) Long-Acting Preparations

- This group includes glargine, detemir, and degludec, all of which provide long-lasting and almost peak-less effects by different mechanisms. They ***mimic 2nd phase.***

Table (14) Monophasic Insulin Preparations in Egypt and their Characteristics

Preparation	Formulations	Onset	Peak	Duration	Regimen	Route
Short and Rapid-Acting Preparations						
Regular ***(Insulin human 2022)***	• Vial 100 Units/mL • Vial 40 Units/mL • Cartridge 100 Units/mL	30 minutes	2-3 hours	8 hours	30 minutes before meals.	IV, SC
Lispro ***(Insulin lispro) 2023)***	• Cartridge 100 Units/mL • Prefilled pen 100 Units/mL • Prefilled pen 200 Units/mL	< 15 minutes	1 – 2 hours	2 – 3 hours	Within 15 minutes before meals *or* immediately after meals.	IV, SC
Aspart ***(Insulin aspart) 2023)***	• Cartridge 100 Units/mL • Prefilled pen 100 Units/mL	< 15 minutes	1 – 2 hours	2 – 3 hours	5 – 10 minutes before meals.	IV, SC

Glulisine ***(Insulin glulisine 2022)***	• Cartridge 100 Units/mL • Prefilled pen 100 Units/mL	< 15 minutes	1 – 2 hours	2 – 3 hours	Within 15 minutes before meals or 20 minutes after starting a meal.	IV, SC
Intermediate-Acting Preparations						
Insulin NPH "Neutral Protamine Hagedorn" ***(Insulin isophane human 2022)***	• Vial 100 Units/mL • Cartridge 100 Units/mL	2 – 4 hours	4 – 12 hours	12 – 18 hours	Once or twice daily.	SC
Long-Acting Preparations						
Detemir ***(Insulin detemir 2022)***	• Prefilled pen 100 Units/mL	4 hours	No peak	24 hours	Once daily: with the evening meal or at bedtime Twice daily: separated by 12 hours.	SC
Glargine* ***(Insulin glargine 2023)***	• Cartridge 100 Units/mL • Prefilled pen 100 Units/mL • Prefilled pen 300 Units/mL*	4 - 6 hours	No peak	24 - 36 hours	Once daily at the same time every day.	SC
Degludec ***(Insulin degludec 2022)***	▪ Prefilled pen 100 Units/mL	4 hours	No peak	42 hours	Once daily at the same time every day.	SC

* The time to onset of action is longer with Glargine U-300 compared to other long-acting insulins (6 hours compared to 4), and its effect lasts for longer (36 hours compared to 24 hours).

2) Premixed Biphasic Insulin Preparations

- Biphasic insulin preparations consist of a mixture of two monophasic insulin types: one type mimics basal insulin secretion and can be either an intermediate or a long-acting insulin analog; while the other mimics prandial insulin secretion and can be either regular insulin or a rapid-acting insulin analog. The short-acting component usually constitutes 25 – 50% of the mixture. Biphasic preparations are suitable for twice-daily regimens and are all given subcutaneously.

Table (15) Biphasic Insulin Preparations in Egypt

Preparation	Formulation	Regimen
Regular Insulin 30%/Insulin NPH 70% ***(Insulin isophane human and insulin human 2022)***	▪ Vial 100 Units/mL ▪ Cartridge 100 Units/mL	30 – 45 minutes before a meal.
Aspart 30%/Aspart NPH 70%	• Cartridge 100 Units/mL • Prefilled pen 100 Units/mL	15 minutes before a meal ***(Center for Drug Evaluation and Research, 2017)***.

Aspart 50%/Aspart NPH 50%	• Prefilled pen 100 Units/mL	15 minutes before a meal ***(Center for Drug Evaluation and Research, 2017)***.
Aspart 30%/Degludec 70% ***Insulin degludec and insulin aspart 2022)***	• Prefilled pen 100 Units/mL	Once or twice daily with any meal. Used in conjunction with short or rapid-acting insulins in T1DM to cover insulin needs for the remaining meals.
Lispro 25%/Lispro NPH 75%	• Cartridge 100 Units/mL • Prefilled pen 100 Units/mL	15 minutes before a meal ***(Center for Drug Evaluation and Research, 2017).***
Lispro 50%/Lispro protamine 50%	• Prefilled pen 100 Units/mL	15 minutes before a meal ***(Center for Drug Evaluation and Research, 2017)***.

Adverse Effects of Insulin Use ***(Insulin isophane human 2022)***

- Injection site reactions: erythema, swelling, lipid hypertrophy at the site of repeated injections.
- Hypoglycemia; is the most common adverse effects of insulins. It can occur due to dosing errors or changes in diet.
- Hypokalemia; as all insulins promote the shift of potassium from the extracellular space into cells.
- Hypersensitivity reactions include anaphylaxis and skin reactions. Hypersensitivity reactions are less common with human insulin than with animal insulin.
- Edema and heart failure when combined with thiazolidinedione (e.g., pioglitazone).

Contraindications to Insulin Use ***(Insulin isophane human 2022)***

- Insulin cannot be used during an episode of hypoglycemia.
- An insulin product should not be given to a patient with known hypersensitivity to that product.

Insulin administration and storage: See the outpatient pharmacists section and *educational material No (5)*

II. Glucagon-like peptide-1 receptor agonists (incretin mimetics)

- This group includes five drugs available in Egypt which are Exenatide, Dulaglutide, Liraglutide, Semaglutide, and Lixisenatide. But Lixisenatide is present only in combination parenteral dosage form with long-acting insulin (Glargine).
- All of them are injectable only but Semalglutide is the only drug in this group that has two dosage forms (oral and parenteral).
- Mechanism of action and common side effects are similar to oral dosage form. *(See table 18)*

III. Combinations of Insulin and Glucagon-Like Peptide-1 Receptor Agonists

- This type of preparation is designed to provide more diabetic control in T2DM patients who are not controlled on basal insulin alone or require aggressive therapy to reduce their HbA1c. GLP-1 RA increases glucose-dependent insulin release, decreases glucagon secretion, and slows down gastric emptying rate ***(Dungan & DeSantis, 2024).***
- Patients should discontinue any basal insulin or GLP-1 RA therapy before using this type of preparation ***(Insulin glargine and lixisenatide 2023).***

Table (16) Combinations of Insulin and Glucagon-Like Peptide-1 Receptor Agonists

	Degludec/ Liraglutide prefilled pens 100 Units/ 3.6 mg *(Insulin degludec and liraglutide 2023)*	**Glargine/ Lixisenatide prefilled pens 100 Units/ 33 µg and 100 Units/ 50 µg** *(Insulin glargine and lixisenatide 2023)*
Regimen	• The recommended starting dose is 16 units (16 units of Degludec and 0.58 mg of liraglutide) given by SC injection at the same time every day. • The maximum daily dose is 50 units (50 units of Degludec and 1.8 mg of Liraglutide).	• For patients inadequately controlled on less than 30 units of basal insulin, the recommended starting dose is 15 units (15 units of Glargine and 5 µg Lixisenatide). • For patients inadequately controlled on 30 – 60 units of basal insulin, the recommended starting dose is 30 units (10 units of Glargine and 10 µg Lixisenatide). • Glargine/ Lixisenatide should be given by SC daily within 1 hour of the morning meal.
Contraindications	• Liraglutide causes thyroid C-cell carcinoma and is contraindicated for patients with personal or family history of medullary thyroid carcinoma. • During episodes of hypoglycemia. • Patients with known hypersensitivity to liraglutide, Degludec, or any of the components of the preparation Patients who require more than 50 units of basal insulin a day, would exceed the maximum daily dose of Liraglutide (1.8 mg) if they use Degludec/ Liraglutide in combination.	• During episodes of hypoglycemia. • Patients with known allergy to Glargine, Lixisenatide, or any of the other components in the preparation.
Adverse Effects	• Risk of thyroid C-cell carcinomas • Pancreatitis • Hypoglycemia • Acute kidney injury • Hypokalemia • Hypersensitivity reactions	• Risk of thyroid C-cell carcinomas • Pancreatitis • Hypoglycemia • Acute kidney injury • Hypokalemia

Switching insulin products

- The advent of insulin analogues and novel insulin delivery devices gives healthcare providers with the opportunity to select from a wide range of products for their patients. In some cases, clinical reasons might prompt healthcare providers to consider changing insulin products in their patients' regimens. This can be either for better outcomes e.g., improved glycemic control and time in target range, or to avoid adverse events e.g., to avoid episodes of hypoglycemia or to avoid pain from large injection volumes by switching to a high-concentration insulin product ***(Mehta et al., 2021)***.
-
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- Patients might need to switch an insulin product for practical reasons e.g., unaffordability due to high cost or loss of insurance, need for a more convenient and easier to use delivery device, or need for a more flexible dosing schedule ***(Mehta et al., 2021)***.
- Patients should not switch their insulin products without supervision from their healthcare provider. However, patients might be forced to use a different insulin product in emergency situations where their insulin product is not available to them for any reason. Patients should be educated on alternative insulin products that they might have to use in case of emergencies. Patients should be instructed to monitor their blood glucose levels closely and to consult their healthcare provider as soon as possible if they use an alternative insulin product (***Center for Drug Evaluation and Research, 2017)***.

Table (17) Recommendations on Switching Insulin Products

Insulin Types	Recommendations and Notes
Switching between insulin products of the same type (substitution)	
From: Regular insulin or rapid-acting analog **To:** Regular insulin or rapid-acting analog (***Center for Drug Evaluation and Research, 2017)***	• Convert on a unit-per-unit basis. [a] • Rapid-acting insulin analogs should be given 10 – 15 minutes before meals, while regular insulin should be given 30 minutes before meals.
From: NPH insulin **To:** NPH insulin ***(Center for Drug Evaluation and Research, 2017)***	• Convert on a unit-per-unit basis. [a]
From: Premixed insulin **To:** Premixed insulin ***(Center for Drug Evaluation and Research, 2017)***	• Convert on a unit-per-unit basis, provided that the ratio of intermediate-acting to short-acting insulin or rapid-acting analog is the same in both products. [a] • Premixed products containing rapid-acting analogs should be administered 10 – 15 minutes before meals, while products containing regular insulin should be administered 30 minutes before meals.
From: Premixed insulin **To:** NPH insulin plus regular insulin or rapid-acting analog <u>Note:</u> in emergency situations when premixed insulin is not available to the patient. ***(Center for Drug Evaluation and Research, 2017; insulin isophane 2022)***	• Calculate the dose of each component based on its ratio in the premixed product, for example, if a patient takes 20 units of a 70/30 premixed insulin: Give 14 units of intermediate-acting insulin. Give 6 units of short-acting insulin or rapid-acting analog. • How to mix insulin before injection (using the previous example): 1. Draw a volume of air equivalent to 14 units and inject it into the intermediate-acting insulin vial, then remove the needle without drawing any insulin.

	2. Draw a volume of air equivalent to 6 units and inject it into the short-acting insulin vial (or the rapid-acting analog). 3. With the needle still in the vial, turn the vial upside down and draw 6 units of insulin. 4. Roll the intermediate-acting insulin vial in your hands to evenly re-disperse the suspension. 5. Draw 14 units from the intermediate-acting insulin vial.
Switching between basal insulin products	
From: NPH insulin **To:** Insulin Detemir ***(Center for Drug Evaluation and Research, 2017; insulin detemir 2022)***	• Insulin detemir can be administered once or twice daily. • If insulin detemir will be given twice daily, convert the dose on a unit-per-unit basis. [a] • If insulin detemir will be given once daily, add the number of units of NPH insulin doses and administer the total daily dose in a once daily injection. • Some type 2 diabetes patients might require higher doses of insulin detemir.
From: NPH insulin **To:** Insulin Glargine U-100 or U-300 ***(Insulin glargine 2023; insulin glargine U-300 2022)***	• If NPH insulin is given once-daily, convert on a unit-per-unit basis. [a] • If NPH insulin is given twice-daily, start treatment with insulin glargine at 80% of the total daily dose.
From: NPH Insulin, Insulin Glargine U-100, Insulin Glargine U-300 **To:** Insulin Degludec ***(Insulin degludec 2022)***	• In adult patients, give the same total daily dose. • In pediatric patients 1 year of age and older, start with 80% of the total daily dose to reduce the risk of hypoglycemia.
From: Insulin Detemir **To:** Insulin Glargine U-100 ***(Insulin detemir 2022; Mehta et al., 2021)***	• Convert on a unit-per-unit basis. [a]
From: Insulin Glargine U-100 **To:** Insulin Detemir ***(Mehta et al., 2021)***	• Convert on a unit-per-unit basis. [a]

a. Switch insulin so that doses and time of administration remain the same.

Points to consider when switching insulin products

- When switching prandial insulin between regular insulin and rapid-acting analogs, make sure to adjust administration times with respect to meals.
- Some insulin pens dial the dose in increments of 1 unit while other dial the dose in increments of 2 units ***(INSULIN PENS 2019)***. When switching from the first to latter, the dose should be rounded up or down to an even number.
- In emergency situations, clinicians should consider an initial 20% dose reduction when switching between insulin products to avoid hypoglycemia ***(Kocurek & Cryar, 2020)***.
- Before mixing insulin products, always refer to package inserts for details on compatibility.
- When switching from premixed insulin, draw the short-acting insulin or the rapid-acting insulin analog into the syringe before the intermediate-acting insulin ***(Center for Drug Evaluation and Research 2017)***.

(B) Oral Antidiabetic Drug Groups

1. Biguanides (metformin)
2. Sulfonylureas
3. Meglitinides (sulfonylurea analogue)
4. Thiazolidinediones (glitazones, insulin sensitizers)
5. Glucagon-like peptide-1 receptor agonists (incretin mimetics): Semaglutide only
6. Dipeptidyl peptidase-4 inhibitors (gliptins)
7. Sodium-glucose cotransporter 2 inhibitors (gliflozins)
8. Alpha-glucosidase inhibitors

Classification of Antidiabetic Drugs ***(Antidiabetic drugs 2024)***

- ***Insulinotropic agents:*** Depend on residual β-cell function, stimulate the secretion of insulin from pancreatic β cells.
  - **Glucose-dependent (GLP-1 agonists, DPP-4 inhibitors)**: Insulin secretion is stimulated by elevated blood glucose levels (postprandially).
  - **Glucose-independent (sulfonylurea, meglitinides):** Insulin is secreted regardless of the blood glucose level, even if blood glucose levels are low which may lead to an increase in the risk of hypoglycemia.
- **Non-insulinotropic agents**
  - Effective in patients with non-functional β cells
  - Not dependent on residual insulin production
  - Agents: Biguanides, SGLT-2 inhibitors, thiazolidinediones, and α-glucosidase inhibitors.

Table (18) Oral Antidiabetic Drug Groups "For more details about drugs refer to Monographs (The Egyptian Drug Formulary – Endocrine Drugs Chapter, on the EDA website)"

Class	Available drugs in Egypt	Mechanism of action	Common/significant side effects
Biguanides ***(Metformin 2024)***	▪ Metformin	▪ Decreasing gluconeogenesis ▪ Increasing peripheral utilization of glucose.	▪ **Gastrointestinal effects** which are dose dose-related such as diarrhea, nausea, flatulence, dyspepsia, vomiting, and abdominal pain. ▪ **Metformin-associated lactic acidosis:** Dose-related and increases with the presence of risk factors such as renal

			impairment and the patient's age ≥65 years. ▪ **Reversible vitamin B12 deficiency** and subsequent anemia and neuropathy after long-term use.
Sulfonylureas **SU** ***(Chlorpropamide 2024; Glibenclamide 2024; Gliclazide 2024; Glimepiride 2024; Glipizide 2024)***	**First generation** ▪ Chlorpropamide **Second generation** ▪ Glyburide "glibenclamide" (Long-acting agent) ▪ Gliclazide ▪Glimepiride ▪Glipizide (short-acting agent)	▪ Augmenting insulin secretion ▪ Extra-pancreatic effect: - Decrease hepatic gluconeogenesis - Increase peripheral insulin sensitivity.	**Incidence differs between members of the class, check each product** ▪ **Gastrointestinal:** Epigastric fullness, heartburn, nausea, vomiting, abdominal pain, constipation, diarrhea, dyspepsia, and vomiting. ▪ **Hypersensitivity reaction** (Sulfonamide allergy). ▪ **Endocrine & metabolic:** Hypoglycemia. ▪ **Nervous system:** Dizziness, drowsiness, headache, nervousness, and tremor
Meglitinides ***(Nateglinide 2024; Repaglinide 2024)***	▪ Nateglinide ▪ Repaglinide	▪ Blocks ATP-dependent potassium channels, facilitating calcium entry through calcium channels so, increased intracellular calcium stimulates insulin release from the pancreatic beta cells. ▪ Insulin release is glucose-dependent.	**Incidence differs between members of the class, check each product** ▪ **Central nervous system:** Headache ▪ **Endocrine & metabolic:** Hypoglycemia ▪ **Respiratory:** Upper respiratory tract infection
Thiazolidinedione **TZDs** (Glitazones, insulin sensitizers) ***(Pioglitazone 2024)***	▪ Pioglitazone	▪ Improving target cell response to insulin ▪ Improve glucose and lipid metabolism	▪ **Cardiovascular:** Edema ▪ **Endocrine and metabolic:** Hypoglycemia ▪ **Respiratory:** Upper respiratory tract infection
Glucagon-like peptide-1 receptor agonists **GLP-1 agonist** (Incretin mimetics) ***(Semaglutide 2024)***	▪ Semaglutide	▪ Increase insulin secretion ▪ Decrease glucagon secretion ▪ Slow gastric emptying ▪ Regulation of appetite and caloric intake.	▪ **Gastrointestinal effects:** Nausea, vomiting, diarrhea, abdominal pain , and constipation.

Dipeptidyl peptidase-4 inhibitors **DPP-4i** (Gliptins) ***(Alogliptin 2024; Linagliptin 2024; Saxagliptin 2024; Sitagliptin 2024; Vildagliptin 2023)***	▪ Alogliptin ▪ Linagliptin ▪ Saxagliptin ▪ Sitagliptin ▪ Vildagliptin	▪ Increase insulin secretion ▪ Decrease glucagon secretion ▪ Decrease hepatic gluconeogenesis	**Incidence differs between members of the class, ckeck each product** ▪ **Endocrine & metabolic:** Hypoglycemia and increased uric acid ▪ **Respiratory:** Nasopharyngitis, upper respiratory tract infection, and cough ▪ **Cardiovascular:** Peripheral edema ▪ **Genitourinary:** Urinary tract infection ▪ **Hematologic & oncologic:** Lymphocytopenia ▪ **Hypersensitivity reaction** ▪ **Nervous system:** Headache ▪ **Gastrointestinal:** Increased serum lipase (>3 × ULN) ▪ **Renal:** Decreased creatinine clearance, renal function abnormality
Sodium-glucose cotransporter 2 inhibitors **SGLTi** (gliflozins) ***(Canagliflozin 2024; Dapagliflozin 2024; Empagliflozin 2024;; Ertugliflozin 2024)***	▪ Canagliflozin ▪ Dapagliflozin ▪ Empagliflozin ▪ Ertugliflozin	▪ Decreased glucose reabsorption from the tubular lumen and lowers the renal threshold for glucose that lead to increase urinary excretion of glucose. ▪ Decrease sodium reabsorption and increases sodium excretion , which may reduce cardiac preload/ afterload, downregulate sympathetic activity, and decrease intraglomerular pressure.	**Incidence differs between members of the class, ckeck each product** ▪ **Endocrine & metabolic:** Dyslipidemia, hypovolemia with increase thirst, Hypoglycemia, hyperkalaemia ▪ **Gastrointestinal:** Nausea, Abdominal pain, constipation ▪ **Genitourinary:** Dysuria, genitourinary fungal infection, increased urine output, urinary tract infection ▪ **Hematologic & oncologic:** Increased hematocrit ▪ **Infection:** Influenza ▪ **Neuromuscular & skeletal:** Back pain, limb pain and injury ▪ **Respiratory:** Nasopharyngitis ▪ **Cardiovascular:** Hypotension ▪ **Hypersensitivity reaction**

			▪ **Nervous system:** Asthenia, falling, and headache
Alpha-glucosidase inhibitors ***(Acarbose 2024)***	▪ Acarbose	▪ Delayed and low intestinal glucose absorption ▪ Decrease carbohydrate breakdown, leads to decreased hyperglycemia and insulin after eating.	▪ **Gastrointestinal:** Flatulence, diarrhea, and abdominal pain ▪ **Hepatic:** Increased serum transaminases

Table (19) Most Important Tips on Antidiabetic Classes adapted from *(ElSayed et al., 2023j; Kurukulasuriya & Sowers, 2010; Liu & Hu, 2022; Packer, 2018; Xu & Rajaratnam, 2017; Samson et al., 2023)*

	Efficacy	Hypoglycemia	Weight effect	ASCVD benefit			Renal benefit	NAFLD ***	Lipid effect
				MACE*	HF**	Stroke			
Insulin (SC. IV)	+++/++++ Up to ~ 4.9 ↓ in HbA1c	Yes (moderate-severe)	Gain	Neutral	Increase the risk moderate	Neutral	Neutral	Neutral	Improved
Biguanide (Oral)	++ ~1.5% ↓ in HbA1c Type 2 only	No	Neutral-slight loss	Potential benefit	Neutral	Neutral	Neutral	Neutral	Improved
SU (2nd generation) **(**Oral)	++ ~ 1–2% ↓ in HbA1c	Yes (moderate-severe)	Gain	Neutral	Neutral	Neutral-	Neutral	Neutral	Small improvements; mainly in TG
Meglitinide (Oral)	+ ↓ in HbA1c 0.1–2.1% **for repaglinide**, 0.2–0.6% **for nateglinide**	Less risk than SU (Mild)	Neutral	Neutral (May ↑ CV events especially when combined with NPH insulin)	Neutral	Neutral	Neutral	Neutral	Poorly quantified
TZDs (Oral)	++ ~ 1-1.5 % ↓ in HbA1c	No (↑ when pioglitazone is combined with insulin or other diabetic medications)	Gain Dose-related due to fluid retention from HF	Potential benefit: Pioglitazone	Increased risk Moderate - severe	Benefit	Neutral	Benefit	Improved HDL and TG, can lower LDL
GLP-1 agonist (SC, oral)	+++ ~1% ↓ in HbA1c	No	Loss Intermediate to very high	Benefit Dulaglutide Liraglutide Semaglutide	Neutral	Benefit Dulaglutide Semaglutide	Benefit Dulaglutide Liraglutide Semaglutide	Benefit	Improved
DPP-4i (Oral)	+ ~0.74% ↓ in HbA1c	No	Neutral	Neutral	Potential moderate risk Saxagliptin	Neutral	Neutral	Neutral	Poorly quantified

SGLTi (Oral)	++ ~ 0.5–0.7% ↓ in HbA1c	No	Loss Intermediate	Benefit Canagliflozin, Empagliflozin	Benefit Canagliflozin, Dapagliflozin, Empagliflozin Ertugliflozin	Possible benefit for hemorrhagic stroke	Benefit Canagliflozin, Dapagliflozin, Empagliflozin	Potential benefit	Modest beneficial effects as ↑ in HDL and ↓ TG
Alpha-glucosidase inhibitors (Oral)	+ ~0.8% ↓ in HbA1c	Unlikely ****	Neutral to Suggested decrease	No sufficient data	No sufficient data	No sufficient data	Neutral	Neutral	Poorly quantified

*MACE: Major adverse cardiovascular events
**HF: Heart failure
***NAFLD: Non-alcoholic fatty liver disease
**** If a patient had a hypoglycemia episode while taking acarbose, **sucrose** does **not** ↑ blood glucose levels if given because acarbose prevents the body from digesting it into monosaccharides; patients **should be given glucose instead.**

Monitoring Patients with Diabetes Mellitus

Table (20) Monitoring Criteria and Frequency* ***adapted*** **from Uptodate** ***(Key components of routine care for people with diabetes mellitus 2024)***

Intervention	Frequency	Notes
Height, weight, BMI	Each visit	-
Blood pressure	Each visit	The blood pressure target is <130/80 mmHg if it is achieved safely.
Dilated eye examination	Annually " less frequent screening (every 2 to 3 years) may be appropriate for some patients (e.g., patients with little or no retinopathy and near-normal A1C levels)."	To be done at the diagnosis of type 2 diabetes, and within 5 years after the diagnosis of type 1 diabetes. To be examined yearly (or more frequently) if retinopathy is present, every 2 to 3 years if no retinopathy is present.
Comprehensive foot examination	Annually	To be examined each physician's visit if a peripheral vascular disease or neuropathy is present.
Dental examination	Annually	Periodontal disease is more severe and may be more common in diabetic people.
Lipid profile	Initially, as indicated	Testing may be infrequent (e.g., every 5 years) in people <40 years of age who do not have dyslipidemia and are not on cholesterol-lowering treatment.
A1C	Every 3 to 6 months	Goal ≤7% (may be lower or greater in certain cases).
Basic metabolic profile	Annually	Includes electrolytes, BUN, creatinine, calcium, and glucose. To be measured more frequently if the patient has chronic renal disease.
Urinary albumin-to-creatinine ratio	Annually	To be done 3-5 years after the diagnosis of type 1 diabetes and at the time of diagnosis in type 2 diabetic patients; protein excretion should also be monitored if persistent albuminuria exists.
Complete blood count, liver tests	Annually	May be needed more often according to case and results.
TSH, vitamin B12	Annually (if indicated)	T1DM: TSH is a routine test. Patients on metformin: Vitamin B12 is a routine test.

* This information may vary according to the physician's evaluation

Complications with Diabetes Mellitus

Complications are divided into:

- ***Acute complications:*** They include hypoglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemic syndrome.
- ***Chronic complications***: They include:
  - Microvascular complications are those long-term complications that affect small blood vessels. They include diabetic kidney disease "nephropathy", diabetic retinopathy, diabetic neuropathy "gastroparesis, sexual dysfunction, and lower limb complication that may lead to amputation".
  - Macrovascular complications are primarily diseases of the coronary arteries, peripheral arteries, and cerebrovasculature. They include atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease.

N.B.:

- Diabetic foot (nerve and/or vascular damage)

Other complications

- Mouth problems "Periodontal Disease (Gum Disease)"
- Infection due to a decrease in the immune system
- Musculoskeletal diseases
- Non Alcoholic Fatty Liver Disease (NAFLD)
- Hearing loss
- Living with diabetes can also affect your mental health. People with diabetes are two to three times more likely to have depression than people without diabetes.

Hypoglycemia

Definition

- Hypoglycemia in diabetic patients is usually defined as any abnormally low plasma glucose concentration (with or without symptoms) exposing the patient to harm ***(Cryer et al., 2024).***
- It is the most common complication of glucose-lowering therapy and a major challenge for glucose management therapy; therefore its occurrence and risk should be evaluated with every patient encounter ***(Cryer et al., 2024; ElSayed et al., 2023e).***
- It predominates in type 1 diabetes as opposed to type 2 diabetes. It is typically only present in those with type 2 diabetes who are on specific medication classes (such as insulin, sulfonylureas, or meglitinides) ***(Cryer et al., 2024).***

Classification

Table (21) Hypoglycaemia Classification ***(ElSayed et al., 2023e)***

	Glycemic criteria/description
Level 1	Glucose < 70 mg/dL and ≥ 54 mg/dL
Level 2	Glucose < 54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for the treatment of hypoglycemia, irrespective of glucose level

N.B.: Caution is advised when considering the results of the blood glucose monitoring (BGM) as it may not be accurate in patients with poor capillary blood flow, such as those with shock, hypothermia, Raynaud phenomenon, or peripheral vascular disease ***(Cryer et al., 2024).***

Signs, symptoms, and screening

- Hypoglycemia causes neurogenic (autonomic) and neuroglycopenic (resulting from the direct central nervous system deprivation of glucose ***(Mathew, 2022)*** symptoms with the latter occurring more commonly in geriatrics and patients with longstanding diabetes ***(Cryer et al., 2024).***

Table (22) Hypoglycaemia Symptoms ***(Cryer et al., 2024)***

Neurogenic Symptoms	Neuroglycopenic Symptoms
Tremor, palpitations, anxiety/arousal, sweating, hunger, and paresthesias	• Dizziness, weakness, drowsiness, delirium, confusion, and, at lower plasma glucose concentrations, seizure, and coma. • Profound, prolonged hypoglycemia can cause brain death if left untreated, but most episodes are reversible after raising the glucose level.

- The onset of symptoms may occur at glucose levels < 70 mg/dL, however, the value differs from one patient to another and within the same patient over time ***(Cryer et al., 2024):***
  - **In patients with chronic hyperglycemia:** the glycemic thresholds for the neurogenic and neuroglycopenic responses shift to higher plasma glucose concentrations.
  - **In patients with repeated hypoglycemia episodes** (caused by intensive treatment): the thresholds shift to lower plasma glucose concentrations.
- Symptoms may not be present due to impaired awareness. Diabetic patients may have blunted responses to hypoglycemia brought on by recent antecedent hypoglycemia, prior exercise, or sleep ***(Cryer et al., 2024).***
- History of hypoglycemia for all individuals at risk for hypoglycemia should be reviewed at each clinical appointment and evaluated as necessary ***(ElSayed et al., 2023e).*** **(C)**
- Clinicians should screen all persons at risk for hypoglycemia for impaired hypoglycemia awareness ***(ElSayed et al., 2023e).*** **(E)**

Risk factors ***(Cryer et al., 2024)***

- **Medications** known to cause hypoglycemia (e.g., insulin, sulfonylureas, meglitinides).

Nocturnal hypoglycemia in Type 1 Diabetes	Occurs less commonly in patients who use rapid-acting insulin analogs (lispro, aspart, glulisine) instead of regular insulin before meals.
	Using long-acting insulin analogs (glargine, detemir, degludec) instead of NPH as the basal insulin confers a slightly lower risk of nocturnal hypoglycemia.
Hypoglycemia with sulfonylureas	Long-acting drugs, such as glibenclamide, are more frequently reported to cause hypoglycemia compared with sulfonylureas of lower risk (e.g., glipizide, glimepiride, and gliclazide).
Medications with low hypoglycemia risk	Agents that do not cause unregulated hyperinsulinemia (e.g., metformin, alpha-glucosidase inhibitors, thiazolidinediones, GLP-1 receptor agonists, dual GLP-1 and GIP receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors)

- **Medication errors** (e.g., inappropriate doses, wrong insulin type)
- **Overcorrection of hyperglycemia** (e.g., intentionally taking additional insulin)
- **Chronic kidney disease**
- **Old-age**
- **History** of hypoglycemia or **impaired** awareness of hypoglycemia
- **Cognitive impairment** or intellectual disability
- **Long-standing** diabetes
- **Alcohol consumption**
- **Irregular** eating schedules and/or eating disorders
- **Fasting**
- **A history** of untreated pituitary, adrenal, or thyroid insufficiency
- **Excessive physical activity**

Prevention

- All people who use insulin **(A)** or are at risk for hypoglycemia **(C)** should get systematic education on hypoglycemia prevention and treatment, with continued education for those who have hypoglycemic episodes ***(ElSayed et al., 2023e).***
- The patient's risk factors contributing to hypoglycemia should be identified to avoid them where possible ***(Cryer et al., 2024).***
- Recommend the regular monitoring of glucose, especially in patients with type 1 diabetes and type 2 diabetes on insulin. Patients may perform BGM before and 2 to 3 hours after each meal, at bedtime, in the middle of the night, and before and after exercise ***(Cryer et al., 2024)***.
- CGM is advised for those at high risk of hypoglycemia ***(ElSayed et al., 2023e).*** **(A)**
- The intermittent use of CGM may be useful for diabetic patients prone to asymptomatic hypoglycemia due to repeated episodes of hypoglycemia and/or impaired awareness of hypoglycemia ***(Cryer et al., 2024).***
- Educate the patients about exercise-induced hypoglycemia, which can occur during, shortly after, or many hours after exercise, and highlight the importance of frequent glucose monitoring ***(Cryer et al., 2024).***
- To reduce the early post-exercise hypoglycemia, intersperse brief episodes of intense exercise, add carbohydrate ingestion (e.g., 1 g/kg/h), and reduce insulin doses ***(Cryer et al., 2024).***
- The patient's medications should be adjusted based on glucose patterns, and the target glucose and A1C levels should be reviewed if needed ***(Cryer et al., 2024).***

- Patients should be referred to their physicians to adjust their medications, meals, and exercise based on their patterns and caregivers should be taught to recognize severe hypoglycemia ***(Cryer et al., 2024).***
- If there are multiple attacks of stage 2 or 3 hypoglycemia, it is important to reevaluate the treatment approach, including adjusting or switching diabetic medications as needed ***(ElSayed et al., 2023e).*** **(E)**

Treatment

- Restoring the normal glucose concentration is the main aim of treatment. This is usually done by administering carbohydrates, IV glucose, or glucagon (to stimulate hepatic glucose production) ***(Cryer et al., 2024).***

Table (23) Hypoglycaemia Treatment Tips that should be Delivered to the Patient

Level 1 (Mild) **70 > BG ≥ 54 mg/dL** The patient is conscious, oriented, and able to swallow	▪ Temporarily avoid tasks requiring alertness such as driving ***(Cryer et al., 2024)***. ▪ Glucose is the preferred treatment, but any carbohydrate with glucose can be utilized ***(ElSayed et al., 2023e)***. **(B)** ▪ Ingest fast-acting carbohydrates (15-20 g), glucose-containing food, or 150-200 ml of pure fruit juice (e.g. orange juice) ***(Graveling et al., 2023).*** ▪ Repeatedly measuring the plasma glucose level within 15 minutes ***(Graveling et al., 2023; ElSayed et al., 2023d)***. If the BG remains < 70 mg/dl repeat the previous steps up to 3 times ***(Graveling et al., 2023).*** ▪ If hypoglycemia still exists, contact healthcare professionals for the possible use of IV glucose or glucagon *(As in Level 3)* ***(Graveling et al., 2023).*** ▪ Insulin and insulin secretagogues may cause recurrent hypoglycemia, therefore the patient may need to eat more food after recovery to prevent the recurrence ***(ElSayed et al., 2023d).*** ▪ Once the blood glucose level improves, the patient should have a meal or a snack (containing 15-20 g of long-acting carbohydrates, or 40 g if IM glucagon has been used) to prevent the recurrence of hypoglycemia ***(Graveling et al., 2023)***. ▪ For patients with enteral tube feeding, they should be administered 20 g quick-acting carbohydrate via enteral tube then the tube is flushed with 40-50 ml water to prevent blockage ***(Graveling et al., 2023).*** ▪ The treatment regimen should be reviewed ***(Cryer et al., 2024).***
Level 2 (Moderate) **BG <54 mg/dL** The patient is conscious and able to swallow but confused, disoriented, or aggressive	▪ Immediately ingest 15 to 20 grams of glucose or fast-acting carbohydrates if the patient is capable and cooperative ***(Graveling et al., 2023).*** ▪ Monitor blood glucose level after 15 minutes ***(Graveling et al., 2023; ElSayed et al., 2023e)***. If <70 mg/dL, repeat treatment up to 3 times ***(Graveling et al., 2023).*** ▪ If hypoglycemia still exists, contact healthcare professionals for the possible use of IV glucose or glucagon *(As in Level 3)* ***(Graveling et al., 2023).*** ▪ Once the blood glucose level improves, take a meal or a snack (containing 15-20 g of long-acting carbohydrates, or 40 g if IM glucagon has been used) to prevent the recurrence of hypoglycemia ***(Graveling et al., 2023).*** ▪ For patients with enteral tube feeding, they should be administered 20 g quick-acting carbohydrate via enteral tube then the tube is flushed with 40-50 ml water to prevent blockage ***(Graveling et al., 2023).*** ▪ **Only pure glucose** should be administered for symptomatic hypoglycemia treatment in patients on insulin or insulin secretagogue together with an alpha-glucosidase inhibitor (e.g., acarbose). This is because table sugar (sucrose) raises blood sugar less effectively as alpha-glucosidase inhibitors slow its digestion ***(Cryer et al., 2024; Graveling et al., 2023).***

	▪ Cognitive impairment is typically present at this hypoglycemic level ***(Cryer et al., 2024).***
Level 3 (Severe) The patient is unconscious, very aggressive, or NPO	▪ **For hospitalized patients**: They should be treated quickly with 25 g of 50% IV **glucose (dextrose)** ***(Cryer et al., 2024)***, they may be given also 100 ml of 20% glucose or 200 ml of 10% glucose over 15 minutes ***(Graveling et al., 2023).*** ▪ **For patients without IV access: Glucagon:** (subcutaneous, intramuscular, or nasal) usually restores the patient's consciousness within approximately 15 minutes, although marked nausea or vomiting may follow ***(Cryer et al., 2024).*** - To prevent these side effects, the patients should immediately administer concentrated oral carbohydrates after the glucagon dose once the consciousness improves before the nausea develops ***(Cryer et al., 2024).*** - **If Glucagon is not available:** Some experts suggested that, pending the arrival of the emergency team, the caregiver may squeeze cake frosting in the space between the teeth and buccal mucosa, while slightly tilting the patient's head to the side. Some also suggest the use of table sugar under the tongue if the cake frosting is not a feasible option ***(Cryer et al., 2024).***
Important Treatment Notes	▪ If measuring plasma glucose is not accessible during an event but neurologic recovery occurs after restoring a normal glucose level, then the event was caused by hypoglycemia ***(Cryer et al., 2024).*** ▪ **Examples of 15-20 g rapid-acting carbohydrates** ***(Graveling et al., 2023)*****:** - 150-200 ml pure fruit juice (e.g., orange juice) - 3-4 full teaspoons of sugar dissolved in water. (Less likely to be effective if the patient is on acarbose). ▪ The patient may need to initiate a continuous infusion of glucose (or food if possible) after the initial treatment as the response to IV glucose and glucagon is transient. ▪ **The follow-up 20 g long-acting carbohydrate snack/meal could include** ***(Graveling et al., 2023)*****:** - 2 biscuits - A slice of bread - 200-300 ml milk - Or next carbohydrate-containing meal ▪ **For level 3:** once glucose is above 70 ml/dl, follow-up treatment can be initiated similarly to levels 1 and 2, but if the patient is NPO, they should be given 10% glucose infusion at 100 ml/hr until no longer NPO or until reviewed by the treating physician ***(Graveling et al., 2023).*** ▪ Further treatment depends on the medication used and the symptoms' severity ***(Cryer et al., 2024).*** ▪ **Glucagon may be ineffective** in malnourished patients, those with severe liver disease, in case of sulfonylurea-induced hypoglycemia, or repeated hypoglycemia. IV glucose would be more suitable ***(Graveling et al., 2023).*** ▪ **Sulfonylurea-induced hypoglycemia** may be long-lasting or recurrent as the sulfonylureas or their metabolites may continue to stimulate insulin secretion even after initial treatment. The hypoglycemia risk may persist for up to 24-36 hours following the last dose, especially if there is concurrent renal impairment ***(Graveling et al., 2023).***

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome

Definition

Diabetic ketoacidosis (DKA) and **Hyperosmolar Hyperglycemic State** (HHS, also known as hyperosmotic hyperglycemic nonketotic state [HHNK]) are two of diabetes' most serious acute complications ***(Hirsch et al., 2024).***

The main differences between DKA and HHS are related to the presence of ketoacidosis and the degree of hyperglycemia. The following table shows the **definitions proposed by the American Diabetes Association (ADA) for DKA and HHS** ***(Kitabchi et al., 2009)*****:**

Table (24) Difference between Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome

	DKA			HHS
	Mild	**Moderate**	**Severe**	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25 to 7.30	7.00 to 7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15 to 18	10 to <15	<10	>18
Urine ketones	Positive	Positive	Positive	Small
Serum ketones – Nitroprusside reaction	Positive	Positive	Positive	≤ Small
Effective serum osmolality (mOsm/kg)◊	Variable	Variable	Variable	>320
Anion gap§	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

◊ Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18.

§ Calculation: (Na+) – (Cl– + HCO3–) (mEq/L).

Euglycemic Ketoacidosis: It is the development of raised anion gap metabolic acidosis, ketonemia (>3.0 mmol/L), or significant ketonuria (2+ or more on standard urine sticks) in diabetic patients despite having a normal glucose level. It's more frequently seen with sodium-glucose cotransporter (SGLT) inhibitors. If SGLT inhibitors precipitate in ketoacidosis, they should be discontinued ***(Dhatariya, 2023).***

Signs and Symptoms *(Aldhaeefi et al., 2022)*

- For DKA and HHS: polyuria, polydipsia, weakness, and changes in mental status.
- Presence of fruity odor in the breath.
- Signs of dehydration, e.g., dry mucous membranes, poor skin turgor, tachycardia, hypotension, and increased capillary refill in severe dehydration.
- Unconsciousness (If DKA is left untreated).

Precipitating Factors *(Kitabchi et al., 2009)*

- **Infection:** is the most frequent trigger for the emergence of DKA and HHS.
- **Insulin omission:** Young adults may omit their insulin because:
  - They fear weight gain or hypoglycemia.
  - They rebel against authority.
  - They suffer from the stress of chronic disease.
- **Inadequate insulin** therapy
- Pancreatitis, myocardial infarction, or cerebrovascular accident
- **Some medications** affect carbohydrate metabolism, e.g., corticosteroids, thiazides, sympathomimetics, conventional antipsychotics, and atypical antipsychotics.
- **Psychological issues** made worse by eating disorders may contribute to recurrent ketoacidosis in young adults with type 1 diabetes.

- **The presence of an underlying illness** that provokes the release of counterregulatory hormones or restricts the patient's ability to access water (e.g., limited mobility, altered response to thirst), may cause severe dehydration and HHS.

Prevention ***(Kitabchi et al., 2009)*****:** Through proper education which includes the following:

- Identify precipitating factor(s) to help avoid them. Moreover, highlight the importance of sticking to the insulin as prescribed and advise against discontinuation without consulting the medical team.
- Educate the patient on the early warning symptoms to promptly contact the healthcare team once needed.
- Educate the caregivers on managing sick days and keeping records; for instance, they should learn how to assess and document temperature, measure blood glucose, and administer insulin.
- Long-term care facility staff should be supervised and educated on recognizing signs of dehydration in elderly patients to help prevent and promptly treat HHS if it occurs.
- Review the patient's blood glucose patterns. A supplemental short- or rapid-acting insulin is used according to the patient's needs.
- Educate the patient on the proper injection techniques, sites, and timing for BGM.
- Educate the patient on the proper storage conditions and ensure insulin effectiveness, e.g., insulin may be expired or denatured. Advise your patient to double-check before reuse. *(Refer to the Pharmacological Treatment of Diabetes Mellitus section of this guide)*
- Advise the patient to consult the healthcare provider if there's a fever or suspected infection.
- Advise the patient to get an easily digestible liquid diet with carbohydrates and salt when nauseated.

Treatment

1) **Home glucose-ketone meters** may aid the patient in the early recognition and management of upcoming ketoacidosis, as they help adjust insulin therapy at home thus reducing hospitalization with DKA ***(Kitabchi et al., 2009).***

2) It is recommended to consult a mental health team for patients with recurrent admissions, as a **psychological element**, such as an eating disorder or other undiagnosed mental disorder, is likely to be present ***(Dhatariya, 2023).***

3) The following algorithm illustrates DKA, and HHS management (Inpatient care) after completing the initial evaluation, checking capillary glucose, serum/urine ketones, and blood for the metabolic profile to confirm hyperglycemia, ketonemia/ketonuria, or hyperosmolarity ***(Kitabchi et al., 2009).***

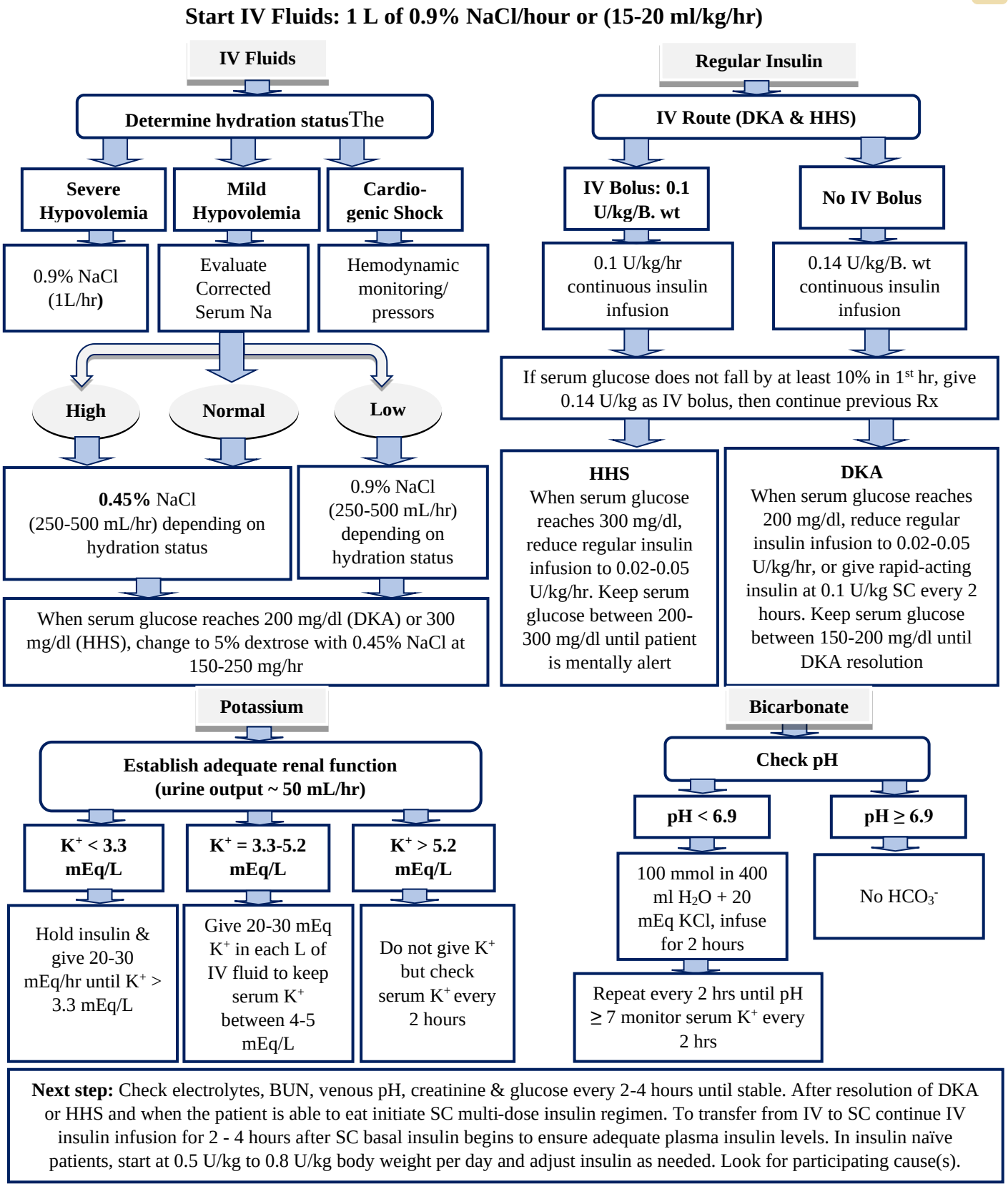


Illustration (8) Protocol for Management of Adult Patients with DKA or HHS adapted from *(Kitabchi et al., 2009)*

Treatment Notes

1) Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose 100 mg/dl, add 1.6 mEq to the sodium value for the corrected serum value ***(Kitabchi et al., 2009).***

2) The patient should be monitored hourly initially to ensure that ketones and/or glucose concentrations are being adequately reduced. Moreover, there should be at least 2 hourly serum potassium and bicarbonate for the first six hours ***(Dhatariya, 2023).***

3) Urinary ketone clearance is not a reliable indicator of ketoacidosis resolution ***(Dhatariya, 2023)***, this is because ß-hydroxybutyrate is converted to acetoacetate and then eliminated in the urine, which gives a false impression that the DKA is taking longer to resolve than it is ***(Dhatariya & Vellanki, 2017).***

4) Fluid therapy ***(Dhatariya, 2023):*** Adequate fluid will resolve the acidosis in DKA

- It aims to restore circulatory volume, clear ketones, and correct electrolyte imbalance.
- An accurate fluid balance chart should be maintained, with a minimum urine output of 0.5 ml/kg/h.
- Disadvantages of 0.9% NaCl infusion solution: Hyperchloraemic metabolic acidosis, which may cause renal arteriolar vasoconstriction resulting in oliguria and a slowing acidosis resolution.
- Caution should be exercised in people with kidney failure, heart failure, or the elderly, as the rate and volume of replacement may need to be adjusted.

5) Insulin therapy ***(Dhatariya, 2023)***

- Critical to suppress ketogenesis, reduce blood glucose, and correct electrolyte disturbance.
- To prepare the insulin infusion, 50 units of human-soluble insulin (0.5 ml) should be mixed with 0.9% sodium chloride solution (49.5 ml). (Concentration: 1 unit/mL).

6) Bicarbonate therapy: Sometimes IV bicarbonate if the pH remains low and inotropesare needed ***(Dhatariya, 2023).***

7) Phosphate use: Despite average whole-body phosphate deficits of 1.0 mmol/kg body weight in DKA, serum phosphate is frequently normal or elevated at presentation. The clinical outcome in DKA has not been improved by phosphate replacement, according to prospective randomized studies, and excessive phosphate therapy can result in severe hypocalcemia. However, in patients with cardiac dysfunction, anemia, or respiratory depression as well as those with serum phosphate concentrations below 1.0 mg/dL, careful phosphate replacement may occasionally be recommended to prevent potential cardiac and skeletal muscle weakness and respiratory depression caused by hypophosphatemia ***(Kitabchi et al., 2009).***

8) **Criteria for resolution of ketoacidosis** ***(Kitabchi et al., 2009):*** include blood glucose < 200 mg/dL and 2 of the following:

- a serum bicarbonate level ≥ 15 mEq/L,
- a venous pH > 7.3, and
- a calculated anion gap ≤12 mEq/L.

9) **Resolution of HHS** is associated with normal osmolality and return to normal mental status ***(Kitabchi et al., 2009).***

10) **Subcutaneous insulin:**

- Can be initiated upon the DKA or HHS resolution, but the insulin infusion should be overlapped with the SC basal insulin for 2 - 4 hours to prevent hyperglycemia or ketoacidosis recurrence ***(Kitabchi et al., 2009).***
- Some recent studies have shown that the early administration of a low dose of basal insulin besides the IV insulin infusion may prevent rebound hyperglycemia without increased risk of hypoglycemia ***(ElSayed et al., 2023i; Dhatariya, 2023).***

11) Initiate thromboprophylaxis during the hospital stay as per patient risk assessment ***(Dhatariya, 2023).***

12) **Euglycemic Ketoacidosis** ***(Dhatariya, 2023)*****:** is treated the same way as hyperglycemic ketoacidosis.

- Start glucose 10% at once at 125 ml/hr as the glucose is < 252 mg/dL
- Begin with 0.1 units/kg/h insulin rate.
- If glucose is falling despite 10% glucose, reduce it to 0.05 units/kg/h to avoid hypoglycemia.

Diabetic Kidney Disease

Definition

- **Diabetic Kidney Disease (DKD)** is a broad term that includes both diabetic nephropathy (DN) and diabetes mellitus and chronic kidney disease (DM-CKD) ***(Bain et al., 2021).***
- **Diabetic Nephropathy (DN):** it is the damage occurring to the glomerular capillaries in diabetic people leading to albuminuria when no other cause of albuminuria could be found ***(Bain et al., 2021).***
- **Diabetes Mellitus and Chronic Kidney Disease (DM-CKD):** The presence of structural renal abnormalities for > 3 months with reduced glomerular filtration in people with diabetes mellitus ***(Bain et al., 2021).***
- DKD occurs in 20 – 40% of diabetic patients, and typically develops after 10 years of type 1 diabetes but may also be found upon the diagnosis of type 2 diabetes ***(ElSayed et al., 2023l).***

Signs, Symptoms, and Screening *(ElSayed et al., 2023l)*

- Patients with DKD typically present with long-standing diabetes, retinopathy, albuminuria without gross hematuria, and gradual loss of eGFR.
- In type 2 diabetes, signs of DKD may be present at the time of diagnosis or without retinopathy.
- Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes.
- Patients with type 1 diabetes who have had the disease for five years or more and all those with type 2 diabetes regardless of treatment should have their urine albumin (such as the spot urinary albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate [eGFR] evaluated at least once a year. **(B)**
- In case of established chronic kidney disease (CKD), urinary albumin (e.g., spot UACR) and eGFR should be monitored 1– 4 times yearly depending on the kidney disease stage. **(B)**

Prevention *(ElSayed et al., 2023l)*

- Blood glucose and blood pressure control are the only well-established measures for the primary prevention of CKD.
- Due to the lack of evidence, the American Diabetes Association does not recommend using renin-angiotensin-aldosterone system (RAAS) inhibitors solely for the prevention of DKD development.

Treatment

1) **RAAS Inhibitors**: RAAS inhibition is the cornerstone for the management of patients with DKD with albuminuria and the treatment of hypertension in diabetic patients (with or without DKD) ***(ElSayed et al., 2023l).***
   - To prevent the kidney disease progression and reduce cardiovascular events, for nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended in case of moderately increased albuminuria (UACR 30–299 mg/g creatinine) **(B)** and is strongly recommended in case of severely increased albuminuria (UACR ≥ 300 mg/g creatinine) and/or eGFR <60 mL/min/1.73 m^2 ***(ElSayed et al., 2023l).*** **(A)**
   - It is not recommended to use an ACE inhibitor or an ARB for CKD primary prevention in normotensive diabetic patients, with normal UACR (<30 mg/g creatinine), and normal eGFR ***(ElSayed et al., 2023l).*** **(A)**
   - **The following illustration summarizes serum creatinine and potassium monitoring during ACE inhibitors or ARBs treatment, in addition to dose adjustment and monitoring of side effects** ***(KDIGO, 2022)***

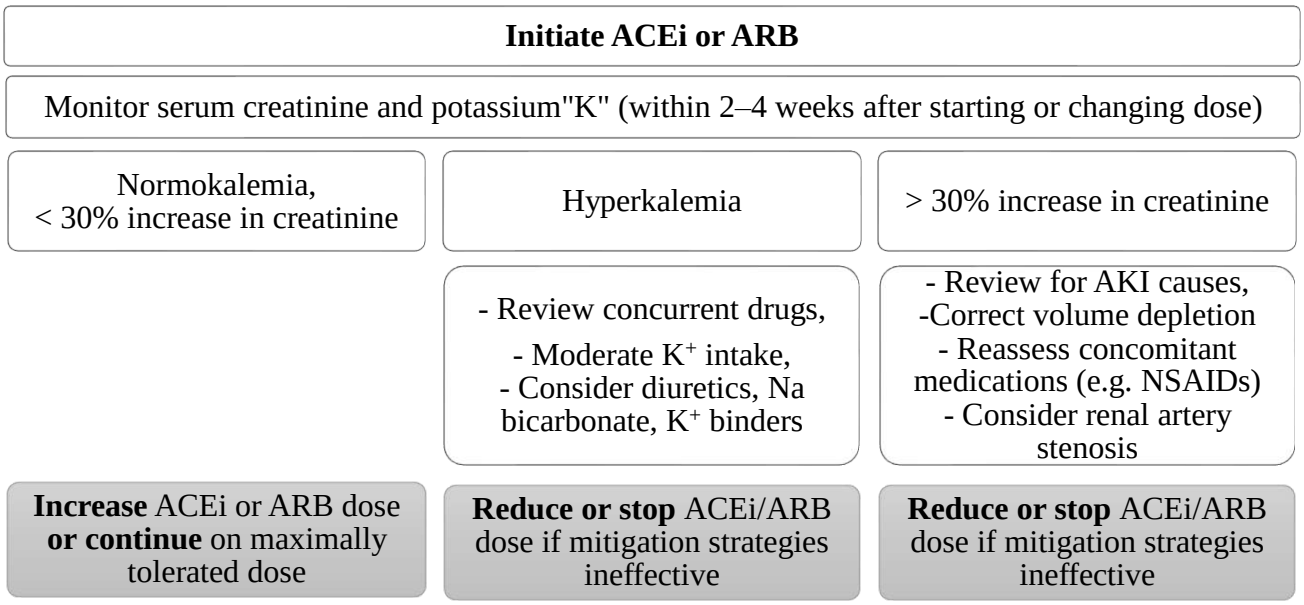


Illustration (9) Essential Monitoring Parameters during ACEi/ARB Treatment adapted from *(KDIGO, 2022)*

2) **Sodium-glucose cotransporter-2 inhibitors (SGLT2i)**

- SGLT2i have direct effects on the kidney, i.e., not mediated through glycemia. They reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss ***(ElSayed et al., 2023l).***
- According to KDIGO 2022, (SGLT2i) is recommended in treating patients with **type 2 diabetes**, CKD, and an eGFR ≥ 20 ml/min/1.73 m^2 ***(KDIGO, 2022).*** **(A)**
- It is appropriate to withhold SGLT2i for patients during times of prolonged fasting, surgery, or critical illness when their risk for ketosis may be higher ***(KDIGO, 2022).***
- Consider lowering thiazide or loop diuretic dose before initiating SGLT2i in patients with a risk for hypovolemia, educate your patients about symptoms of volume depletion and hypotension, and follow up on their volume status after starting the medication ***(KDIGO, 2022).***
- If the patient is already on SGLT2i, it is appropriate to continue the medication even if the eGFR drops below 20 ml/min per 1.73 m^2 unless it is not tolerated or kidney replacement therapy is needed ***(KDIGO, 2022).***
- **Periprocedural/perioperative care** ***(KDIGO, 2022)***
  - Patients should be informed about the possible risks of DKA.
  - Withhold SGLT2i the day of same-day procedures and limit fasting as much as possible.
  - Discontinue SGLT2i 3–4 days before surgery, and measure blood glucose and ketone levels upon admission (The procedure or surgery should be conducted if the patient is clinically well, and ketones are <1.0 mmol/l).
  - Restart SGLT2i post-surgery only when the patient can eat and drink normally.
- **Selection of Glucose-Lowering Medications for T2DM Patients with CKD**

  Some factors should be taken into consideration when selecting a glucose-lowering medication for patients with type 2 diabetes and CKD, which include medication limitations with reduced eGFR, and their effect on CKD progression, CVD, and hypoglycemia ***(ElSayed et al., 2023l).***
  - The combination of metformin and SGLT2i is beneficial for most patients with type 2 diabetes, CKD, and eGFR ≥ 30 ml/min per 1.73 m^2 ***(KDIGO, 2022).***

- It is recommended to use a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) for patients who fail to achieve their glycemic targets despite using metformin and SGLT2i, or who are unable to use these medications ***(KDIGO, 2022).*** **(A)**

  - **The following illustration shows the practical approach to starting SGLT2i in patients with type 2 diabetes and CKD** ***(KDIGO, 2022):***

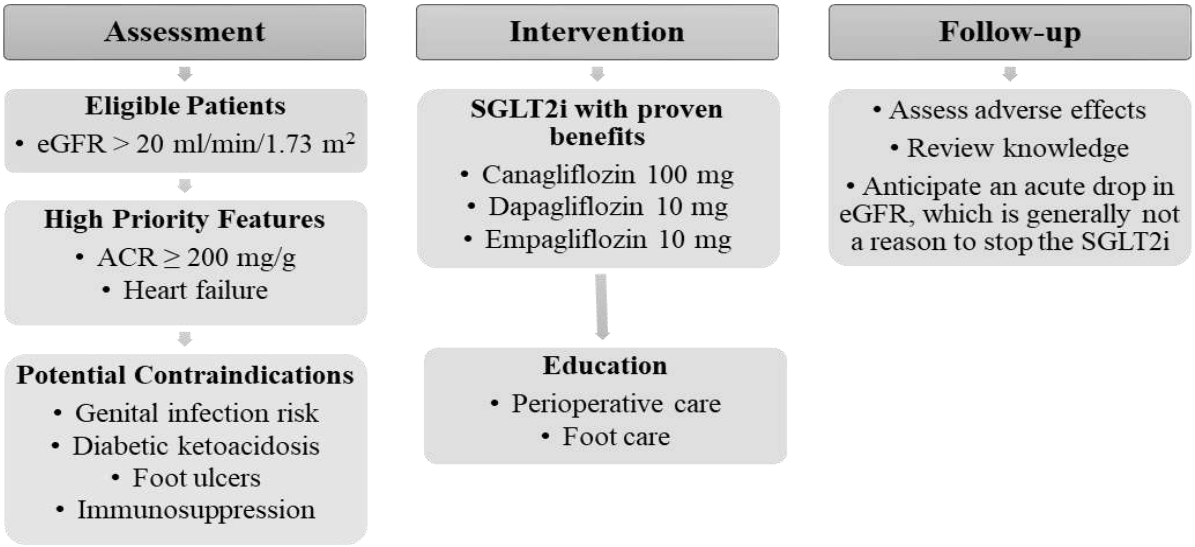


Illustration (10) SGLT2i Use in Chronic Kidney Disease adapted from *(KDIGO, 2022)*

3) **Nonsteroidal mineralocorticoid receptor antagonist (MRA)**
   - To reduce cardiovascular events and CKD progression (if eGFR is ≥ 25 mL/min/1.73 m^2), a nonsteroidal MRA that is effective in clinical trials is recommended while monitoring potassium levels ***(ElSayed et al., 2023l).*** **(A)**
   - A nonsteroidal MRA, such as finerenone, can be added to a RAAS inhibitor and an SGLT2i ***(KDIGO, 2022).***
   - Novel nonsteroidal MRA has been shown to reduce albuminuria similarly to steroidal MRA with a lesser risk of hyperkalemia, and it is more selective for mineralocorticoid receptors ***(KDIGO, 2022).***
   - **The following illustration shows s**erum K^+ monitoring during treatment with finerenone. Adapted from the protocols of Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) ***(KDIGO, 2022):***

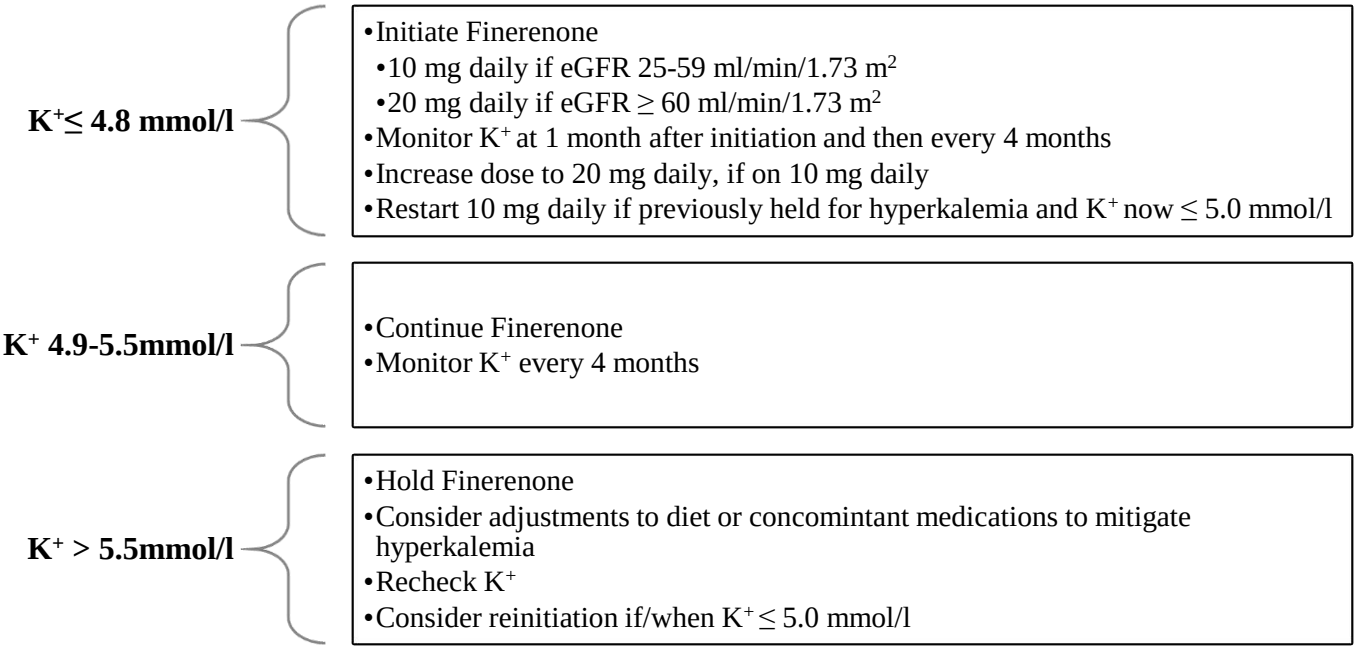


Illustration (11) Finerenone Use and Adjustment with Potassium Level adapted from *(KDIGO, 2022)*

Diabetic Retinopathy

Definition

Diabetic retinopathy is a chronic progressive disease of the retinal microvasculature that may threaten the patient's eyesight. It is associated with prolonged hyperglycemia and other diabetes-linked conditions such as hypertension ***(Ghanchi et al., 2012).*** Classically, diabetes has been thought of as a microvascular disease of the retina, however, mounting evidence reveals that retinal neurodegeneration is an early event in the pathogenesis of diabetic retinopathy contributing to microvascular abnormalities development ***(Flaxel et al., 2020).***

Diabetic retinopathy is the leading cause of new blindness cases in adults between 20–74 years in developed countries. Glaucoma, cataracts, and other eye disorders are more frequently seen in diabetic patients ***(ElSayed et al., 2023m).***

Signs, Symptoms, and Screening

Diabetic retinopathy may be asymptomatic for years, even at an advanced stage, so screening is essential to identify, monitor, and guide the treatment of the disease ***(Flaxel et al., 2020).***

- **For type 1 diabetes:** An initial dilated and comprehensive eye examination should be conducted *within 5 years* post the diabetes onset ***(ElSayed et al., 2023m).*** **(B)**
- **For type 2 diabetes:** An initial dilated and comprehensive eye examination should be conducted *at the time of diagnosis* ***(ElSayed et al., 2023m).*** **(B)**
- In the absence of any evidence of retinopathy for ≥ 1 annual eye exam and the patient's glycemia is well-controlled, screening may be considered every 1–2 years. However, if any level of diabetic retinopathy is detected, dilated retinal examinations should be conducted at least every year ***(ElSayed et al., 2023m).*** **(B)**
- The more progressive or threatening the retinopathy, the more frequent the examinations required ***(ElSayed et al., 2023m).*** **(B)**
- Patients with preexisting type 1 or type 2 diabetes should have their eyes examined before pregnancy, during the first trimester then periodically every trimester, and for 1 year after delivery depending on the degree of retinopathy ***(ElSayed et al., 2023m).*** **(B)**

Prevention ***(Flaxel et al., 2020)***

- Proper screening and early intervention can prevent severe visual loss; however, it is not possible to prevent diabetes complications in all patients.
- Educate the patients on the importance of maintaining good control of their glucose level and blood pressure to lower the risk of retinopathy development and/or progression.
- HbA1c of 7% or lower is the recommended glycemic target for most patients. Furthermore, in certain cases, patients may benefit from a lower target of 6.5%. The risk of diabetic macular edema (DME) increases with the increase of HbA1c.

Treatment

- The main objectives of diabetic retinopathy treatment include ***(D'Amico et al., 2024):***
  - Vision improvement
  - Vision preservation
  - Delay and reduction of the progression of retinopathy, vitreous hemorrhage, and macular edema
- The treatment of diabetic retinopathy includes both surgical and pharmacologic interventions, an ophthalmologist will guide the proper plan for the patient as required ***(D'Amico et al., 2024).***
- If there is any level of diabetic macular, moderate, or worse non-proliferative diabetic retinopathy or any proliferative diabetic retinopathy, the patient must be immediately referred to an ophthalmologist experienced in diabetic retinopathy management ***(ElSayed et al., 2023m).*** **(A)**

- Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) are the first-line therapy for most cases of diabetic macular edema involving the foveal center and impairing vision acuity ***(ElSayed et al., 2023m).*** **(A)**
  - Patients treated with VEGF inhibitors need frequent follow-up appointments as they may need multiple injections for months to years ***(D'Amico et al., 2024).***
  - Currently, the five anti-VEGF agents commonly used to treat eyes with central-involved diabetic macular edema are bevacizumab, ranibizumab, aflibercept, brolucizumab, and faricimab ***(ElSayed et al., 2023m).***
  - Patients with persistent diabetic macular edema despite the use of anti-VEGF may benefit from macular laser photocoagulation or corticosteroids intravitreal therapy. Both of these therapies are also suitable first-line therapies for patients who cannot take anti-VEGF because of systemic considerations such as pregnancy ***(ElSayed et al., 2023m).***
- Using aspirin therapy, for cardio-protection, is not contraindicated in patients with retinopathy as it does not increase the retinal hemorrhage risk ***(ElSayed et al., 2023m; Flaxel et al., 2020).*** **(A)**
- The addition of fenofibrate to the treatment regimen of patients with dyslipidemia may slow the progression of retinopathy, especially in patients with very mild non-proliferative diabetic retinopathy at baselines ***(ElSayed et al., 2023m).***

Diabetic Neuropathy

Definition ***(Pop-Busui et al., 2016)***

Diabetic neuropathies are the most common long-term complications of diabetes. It is a heterogeneous group of conditions affecting various parts of the nervous system leading to diverse clinical symptoms.

Among the various forms of diabetic neuropathy, chronic distal symmetric polyneuropathy (DSPN) is the most common.

DSPN is the presence of symptoms and/or signs of peripheral nerve dysfunction in diabetic patients in the absence of any other causes. It is the most important cause of foot ulceration.

Screening ***(ElSayed et al., 2023m)***

- All patients with diabetes should be assessed for diabetic peripheral neuropathy **(B)** and signs and symptoms of autonomic neuropathy **(E)** at the time of diagnosis (for type 2 patients) or 5 years after diagnosis (for type 1 patients) and at least annually thereafter.
- Symptoms and signs of autonomic neuropathy should also be assessed if there is evidence of other microvascular complications, such as kidney disease and diabetic peripheral neuropathy. The patient should be asked about orthostatic dizziness, syncope, or dry cracked skin in extremities.
- Patients with diabetic neuropathy, retinopathy, and/or nephropathy should have their gastroparesis assessed, and symptoms such as early satiety, unexpected glycemic variability, bloating, nausea, and vomiting should be looked for. **(C)**
- Erectile dysfunction should be annually screened for men with other forms of diabetic neuropathy. **(C)**
- Female patients who have other forms of diabetic neuropathy should be assessed for lower urinary tract symptoms and sexual dysfunction in the presence of recurrent urinary tract infections. **(E)**

Prevention ***(ElSayed et al., 2023m)***

- Glycemic control is the cornerstone of the prevention of diabetic peripheral neuropathy (DPN) and cardiac autonomic neuropathy (CAN) in type 1 diabetic patients, whereas it may only modestly delay their progression in type 2 diabetic patients. Unfortunately, if a neuronal loss occurs, it cannot be reversed.
- Other modifiable risk factors, such as dyslipidemia and hypertension should be addressed as a possible way of preventing DPN progression in type 2 diabetic patients and may slow down its progression in type 1 diabetic patients.

Classification ***(Pop-Busui et al., 2016)***

Table (25) Diabetic Neuropathy Classifications

Neuropathies in Diabetes		
Diabetic Neuropathies	Diffuse Neuropathy	DSPN - Primarily small-fiber neuropathy - Primarily large-fiber neuropathy - Mixed small- and large-fiber neuropathy (most common)
		Autonomic (Cardiovascular) - Reduced Heart Rate Variability (HRV) - Resting tachycardia - Orthostatic hypotension - Sudden death (malignant arrhythmia)
		Gastrointestinal - Diabetic gastroparesis (gastropathy)

		- Diabetic enteropathy (diarrhea) - Colonic hypomotility (constipation)
		Urogenital - Diabetic cytopathic (neurogenic bladder) - Erectile dysfunction - Female sexual dysfunction
		Sudomotor dysfunction - Distal hypohidrosis/anhidrosis (inability to sweat when it is hot) - Gustatory sweating (food-related sweating, sometimes called Frey's syndrome)
		Hypoglycemia unawareness
		Abnormal pupillary function
	Mononeuropathy (Atypical forms)	Isolated cranial or peripheral nerve
		Mononeuritis multiplex
	Radiculopathy (Atypical forms)	Radiculoplexus neuropathy
		Thoracic radiculopathy
Non-diabetic Neuropathies		Pressure palsies
		Chronic inflammatory demyelinating polyneuropathy
		Acute painful small-fiber neuropathies (treatment-induced)

Signs and Symptoms

- Asymptomatic diabetic peripheral neuropathy may account for up to 50% of cases. This confers a risk for diabetic patients since if neuropathy is not recognized and no preventive foot care is implemented, they will become exposed to injuries, diabetic foot ulcers, and amputations ***(ElSayed et al., 2023m).***

DSPN

- Different symptoms may occur depending on the class of sensory fibers affected. Characteristically, the pain is burning, lancinating, tingling, or shooting (electric shock-like); it often coexists with paresthesias; and it usually gets worse at night ***(Pop-Busui et al., 2016).***
- Neuropathic pain may be accompanied by allodynia, which is pain brought on by contact with objects such as socks, shoes, or bedclothes, as well as hyperalgesia, which is an excessive response to painful stimuli ***(Pop-Busui et al., 2016).***
- Large fiber involvement may result in tingling without pain, numbness, and loss of protective sensation (LOPS). LOPS is a risk factor for diabetic foot ulceration ***(Pop-Busui et al., 2016).***

Autonomic Neuropathy

- The major clinical manifestations of autonomic neuropathy include the following: resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating ***(ElSayed et al., 2023m).***

Treatment

Pain *Management (DSPN)*

- For the initial pharmacologic treatment for neuropathic pain in diabetes, gabapentinoids, serotonin or epinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended ***(ElSayed et al., 2023m).*** **(A)**
- Pregabalin or duloxetine are initially considered for the symptomatic treatment of neuropathic pain in diabetes ***(Pop-Busui et al., 2016).*** **(A)**
- Gabapentin may also be used effectively as an initial course of treatment, considering patients' socioeconomic status, comorbidities, and possible drug interactions ***(Pop-Busui et al., 2016).*** **(B)**
- Tricyclic antidepressants (e.g., Amitriptyline) may also be used for neuropathic pain in diabetes but with caution as they confer a higher risk of serious side effects ***(Pop-Busui et al., 2016).*** Anticholinergic side effects may be dose limiting and restrict use in individuals ≥ 65 years of age ***(ElSayed et al., 2023m).***
- Use tricyclic antidepressants cautiously in patients with known or suspected cardiac disease because of the possible cardiotoxicity ***(Pop-Busui et al., 2016).***
- Sodium channel blockers include lamotrigine, lacosamide, carbamazepine, oxcarbazepine, and valproic acid ***(ElSayed et al., 2023m).***
- Opioids are not recommended, despite their effectiveness, for the treatment of painful DSPN ***(ElSayed et al., 2023m; Pop-Busui et al., 2016)*** unless other agents have failed ***(Pop-Busui et al., 2016)***. This is because they confer a high risk of addiction, abuse, sedation, and other complications and psychosocial issues even when used for a short term ***(ElSayed et al., 2023m; Pop-Busui et al., 2016).***
- Neuropathic pain can be treated using combination therapy, including combinations with opioids, at lower doses. Referral to specialized pain clinics is required for patients who do not respond to all other combinations and need the addition of opioids to minimize the associated risks of opioid use. ***(Pop-Busui et al., 2016).***
- Although α-Lipoic acid is not approved for the treatment of painful DPN, it may be effective and considered for the treatment of painful DPN ***(ElSayed et al., 2023m).***

Cardiac Autonomic Neuropathy (CAN)

- The main goal of CAN treatment is typically symptom relief, and it should be tailored to the specific clinical manifestation ***(Pop-Busui et al., 2016).***
- ***Orthostatic hypotension*** symptomatic treatment involves both pharmacological and non-pharmacological interventions:
  - Educate the patient on the importance of exercise and physical activity to prevent deconditioning, which is known to make orthostatic intolerance worse ***(ElSayed et al., 2023m; Pop-Busui et al., 2016).***
  - Volume repletion with fluids and salt is the cornerstone management of orthostatic hypotension ***(ElSayed et al., 2023m; Pop-Busui et al., 2016).***
  - In some individuals, low-dose fludrocortisone may be useful in volume repletion, however, they are thought to confer the risk of supine hypertension ***(Pop-Busui et al., 2016).***
  - For patients whose orthostatic hypotension symptoms are not controllable despite using other measures, sympathomimetic medications, such as midodrine, can be used. To reduce the risk of supine hypertension by midodrine, it should be gradually titrated and used only when patients intend to be upright or seated ***(Pop-Busui et al., 2016).***

Diabetic Gastroparesis

- Advise patients to eat multiple small meals of a low-fat low-fiber diet with a higher percentage of liquid calories ***(ElSayed et al., 2023m; Pop-Busui et al., 2016).***

- It is also advised to withdraw medications that affect gastrointestinal motility including opioids, anticholinergics, tricyclic antidepressants, glucagon-like peptide 1 receptor agonists, and possibly dipeptidyl peptidase 4 inhibitors ***(ElSayed et al., 2023m; Pop-Busui et al., 2016).***
- Metoclopramide, a prokinetic agent, is considered for severe gastroparesis that does not respond to other therapies ***(ElSayed et al., 2023m; Pop-Busui et al., 2016).*** It should be taken into consideration that it confers a risk for serious adverse effects (extrapyramidal symptoms), therefore the FDA does not recommend its use beyond 12 weeks duration ***(ElSayed et al., 2023m).***
- Domperidone and erythromycin are other possible options that are used only for a short duration due to tachyphylaxis ***(ElSayed et al., 2023m).***

Erectile dysfunction

- Phosphodiesterase type 5 inhibitors are considered first-line therapy. Transurethral prostaglandins and intracavernosal injections are used in more advanced cases ***(Pop-Busui et al., 2016).***

Cardiovascular Diseases

Definition and notes ***(ElSayed et al., 2023k)***

Diabetic patients are more likely to develop atherosclerosis and silent ischemia.
Atherosclerotic cardiovascular disease (ASCVD) is the primary cause of morbidity and mortality in diabetic patients. It is defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease thought to be of atherosclerotic origin.
Diabetic patients are twice as likely as non-diabetics to develop heart failure, whether with a preserved ejection fraction (HFpEF) or a reduced ejection fraction (HFrEF).
Common concomitant diseases with type 2 diabetes (e.g., hypertension and dyslipidemia) are established risk factors for ASCVD, and diabetes itself provides independent risk.
Screening for peripheral arterial disease (PAD) with ankle-brachial index testing is recommended for asymptomatic diabetics of the age of ≥50 who have microvascular disease in any location, foot complications, or diabetes-related end-organ damage. **(A)**
Individuals who have had diabetes for ≥10 years should be screened for PAD. **(B)**
All persons with diabetes >50 years of age should get noninvasive arterial investigations. If the results are normal, they should be repeated every five years to screen for peripheral arterial disease.

Signs and symptoms

Depends on the disease and complications from ASCVD.

Prevention and management ***(AHA, 2024a; AHA, 2024b; ElSayed et al., 2023k)***

For prevention and management of both ASCVD and heart failure:

1) Cardiovascular risk factors should be evaluated at least once a year; these risk factors include:
   - Duration of diabetes
   - Obesity/overweight
   - Hypertension
   - Dyslipidemia
   - Smoking
   - A family history of premature coronary disease
   - Chronic kidney disease (CKD), and the presence of albuminuria
2) Modifiable abnormal risk factors should be addressed and evaluated as well.
3) Lifestyle therapy involves reducing excess body weight through caloric restriction, engaging in at least 150 minutes of moderate-intensity aerobic activity per week, limiting sodium intake (<2,300 mg/day), increasing consumption of fruits and vegetables (8-10 servings per day) and low-fat dairy products (2-3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day for men and 1 serving per day for women), and increasing activity levels.
4) Glycemic management with recommended medications that had cardiovascular and kidney benefits as previously mentioned.
5) Blood pressure control.
6) Lipid management

Treatment

Hypertension management in diabetic patients *(ElSayed et al., 2023k)*

- All individuals with diabetes and hypertension should monitor their blood pressure at home. **(A)**
- Blood pressure targets for patients with diabetes and hypertension should be individualized through a joint decision-making process that considers cardiovascular risk, potential side effects of antihypertensive drugs, and patient preferences. **(B)** "Treatment should not be aimed at <120/80 mmHg because a mean achieved blood pressure of <120/80 mmHg has been linked to adverse events".
- For persons with blood pressure >120/80 mmHg, lifestyle interventions should be considered such as weight reduction when indicated, using (DASH)- a style eating pattern including lowering sodium and increasing potassium consumption, moderation of alcohol consumption, and increased physical activity. **(A)**
- Individuals with diabetes and hypertension are eligible for antihypertensive medication therapy if their blood pressure is persistently elevated ≥ 130/80 mmHg (based on the average of two or more measurements taken two or more times). If safely achieved, the on-treatment target blood pressure goal is <130/80 mmHg. **(A)**
- Individuals with confirmed office-based blood pressure ≥150/90 mmHg should begin and titrate two medications or a single-pill combination of drugs that have been shown to reduce cardiovascular events in adults with diabetes in addition to lifestyle interventions. **(A)**
- Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) at the maximum tolerated dose are considered as first-line treatment for hypertension in persons with diabetes and coronary artery disease or urinary albumin-to-creatinine ratio ≥300 mg/g creatinine. **(A)** However, individuals with diabetes and the urinary albumin-to-creatinine ratio of 30–299 mg/g creatinine. **(B)** If one class is not tolerated, the other should be substituted. **(B)**
- In most cases, multiple medication therapy is required to attain blood pressure goals. However, combinations of ACEIs and ARBs as well as combinations of ACEIs or ARBs with direct renin inhibitors should be avoided. **(A)**
- Serum creatinine/estimated glomerular filtration rate and serum potassium levels should be evaluated within 7–14 days after starting treatment and at least once a year in patients using ACEIs, ARBs, or diuretics. **(B)**
- Individuals with hypertension who are not meeting blood pressure goals on 3 antihypertensive drugs (including a diuretic) may benefit from mineralocorticoid receptor antagonists (MRA) treatment addition. **(A)**
- B-blockers should be used in hypertensive and diabetic patients with active angina or HFrEF and for 3 years after MI in those with preserved left ventricular function.
- **The following algorithm illustrates the optimal approach to hypertension management in diabetic patients:**

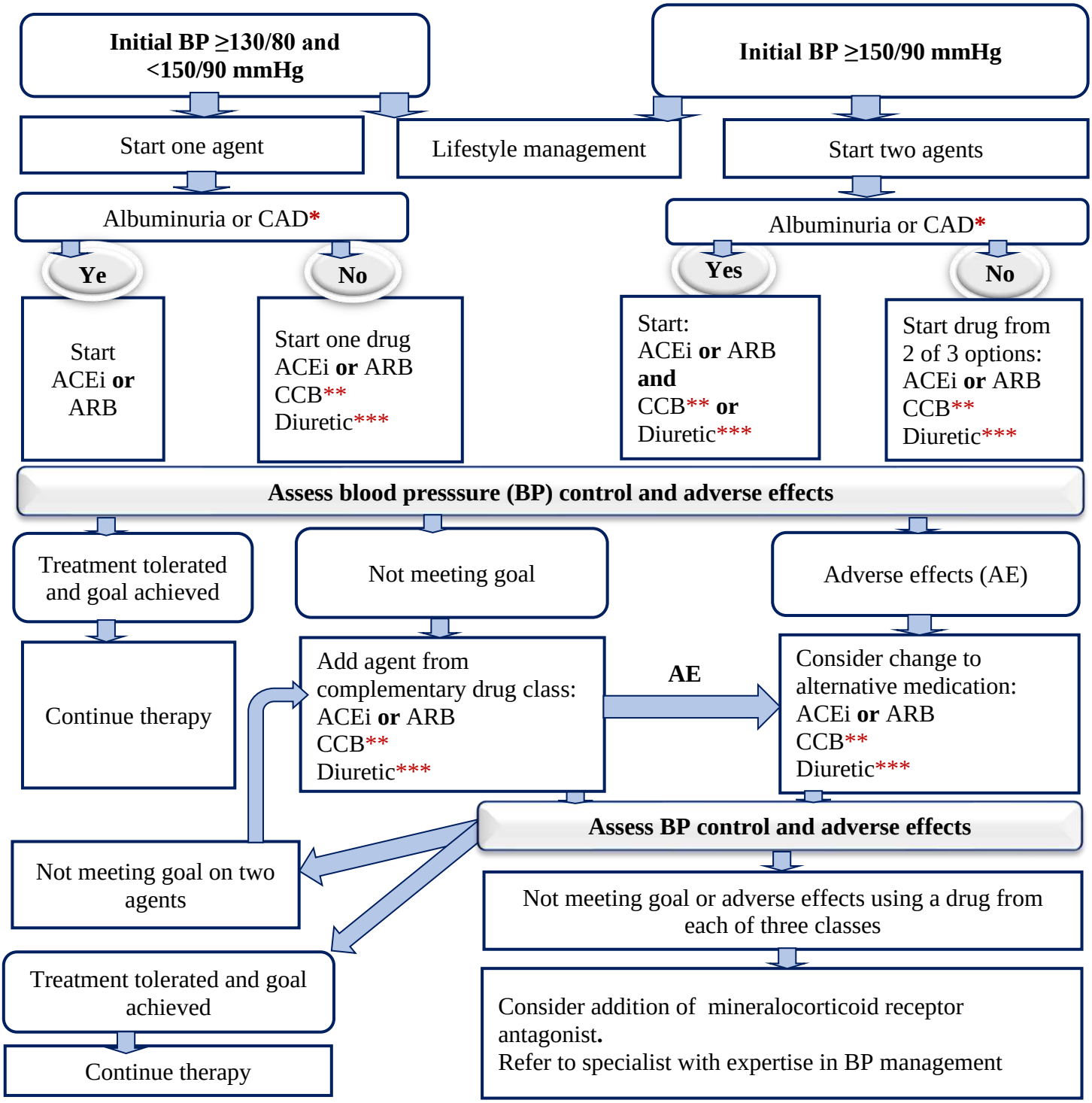


Illustration (12) Hypertension Management in Diabetic Patients adapted from *(ElSayed et al., 2023k)*

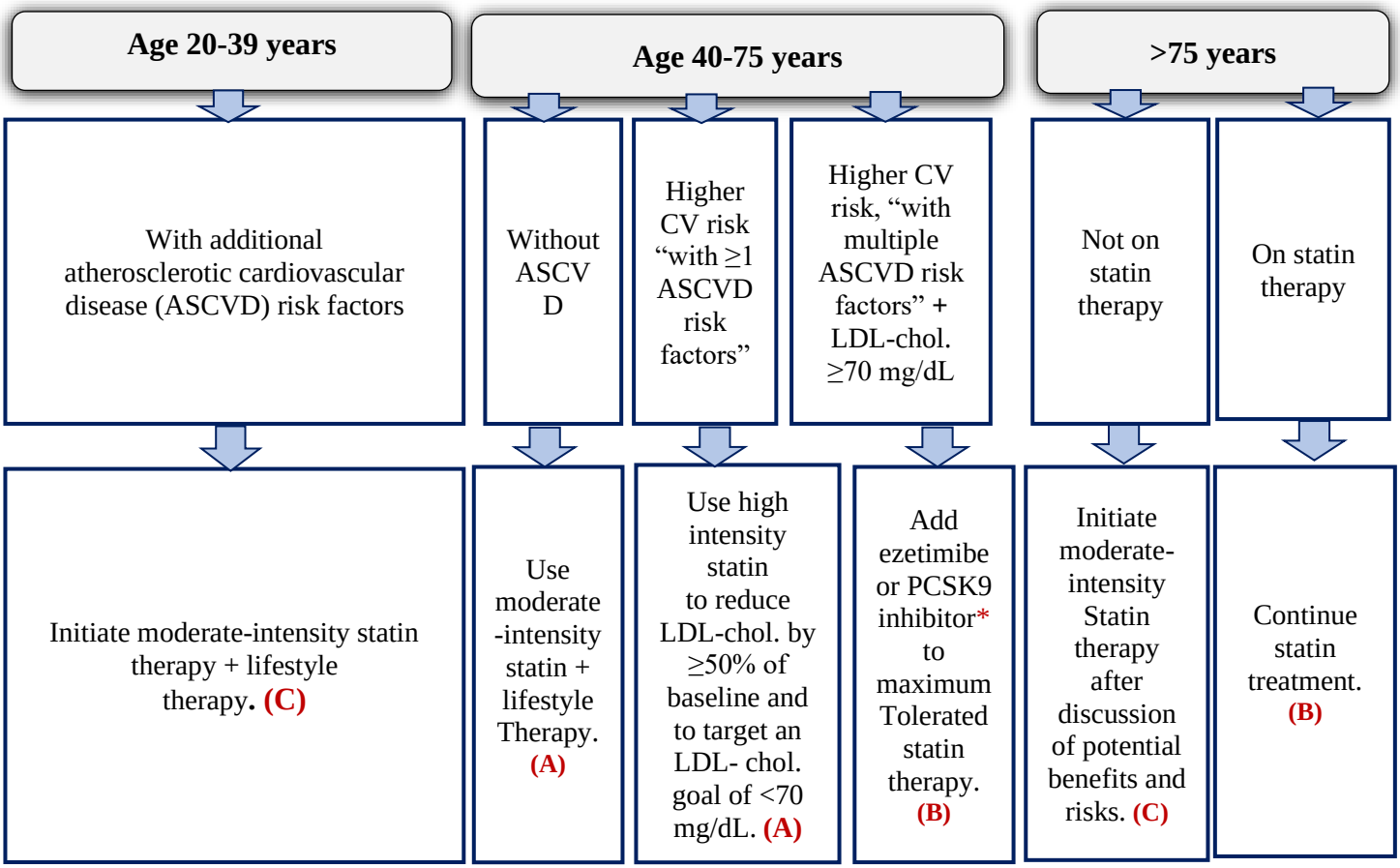
*An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension in people with albuminuria or coronary artery disease (CAD).

**Dihydropyridine calcium channel blocker (CCB).

***Thiazide-like diuretics; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred.

Lipid management in diabetic patients ***(ElSayed et al., 2023k)***

- To improve the lipid profile and lower the risk of developing atherosclerotic cardiovascular disease in diabetic people, lifestyle modification emphasis on weight reduction (if indicated); implementation of a Mediterranean or (DASH) eating pattern; lowering of saturated fat and trans fat; an increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended. **(A)**
- The patient should intensify lifestyle modification and improve glycemic control for patients with elevated triglyceride levels ≥150mg/dL and/or low HDL cholesterol <40 mg/dL for men, <50 mg/dL for women. **(C)**
- In individuals who are not taking statins or other cholesterol-lowering agents, it is reasonable to acquire a lipid profile at the time of diabetes diagnosis, at an initial medical examination, every year after that, or at least every 5 years if the patient is under the age of 40, or more frequently if required. **(E)**
- The patient should do a lipid profile at starting statins or other lipid-lowering therapy, 4–12 weeks after starting or changing doses, and every year after that, as it may help to evaluate the response to therapy and inform medication use. **(A)**
- **Primary prevention in diabetic patients occurs as follows** ***(ElSayed et al., 2023k):***



***PCSK9 inhibitors** (proprotein convertase subtilisin/kexin type 9): Evolocumab and Alirocumab

Illustration (13) Primary Prevention in Diabetic Patients

N.B.: For diabetics who cannot tolerate statin therapy, Bempedoic acid treatment can reduce cardiovascular events as an alternative cholesterol-lowering option. **(A)**

- **Secondary prevention in diabetic patients** ***(ElSayed et al., 2023k)***
  - High-intensity statin medication should be used with lifestyle therapy for persons of all ages with diabetes and atherosclerotic cardiovascular disease. **(A)**
  - For persons with diabetes and atherosclerotic cardiovascular disease, management with high-intensity statin medication is suggested to lower an LDL-cholesterol level by ≥50% from baseline and an LDL-cholesterol goal of <55 mg/dL. If this goal is not achieved on maximum tolerated statin medication, the addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is suggested. **(B)**
  - If persons do not tolerate the intended intensity, the maximum tolerated statin dose should be used. **(E)**
  - For diabetic patients with ASCVD who are intolerant to statin therapy, use Alirocumab or Evolocumab (PCSK9 inhibitor, fully-humanized monoclonal antibodies), **(A)** Bempedoic acid therapy, **(A)** or Inclisiran (PCSK9 inhibitor, a small interfering mRNA that inhibits the intracellular synthesis of PCSK9) **(E)** as alternative cholesterol-lowering medications.

Table (26) Statin Therapy Used for Prevention adapted from (*ElSayed et al., 2023k*)

High-intensity and moderate-intensity statin medications*	
High-intensity statin therapy (lowers LDL cholesterol by ≥ 50%)	**Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)**
Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Pitavastatin 1–4 mg
*Once-daily dosing. XL, extended-release.	

- **Treatment of hypertriglyceridemia in diabetic patients** ***(ElSayed et al., 2023k)***
  - For people with fasting triglyceride levels ≥500 mg/dL, secondary causes of hypertriglyceridemia should be assessed and medical therapy should be considered to lower the risk of pancreatitis. **(C)**
  - In people with moderate hypertriglyceridemia (fasting or non-fasting triglycerides 175 – 499 mg/dL), physicians should evaluate and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides. **(C)**
  - The addition of icosapent ethyl should be considered in people with ASCVD or other cardiovascular risk factors on a statin with controlled LDL-cholesterol but elevated triglycerides (135–499 mg/dL) to reduce cardiovascular risk. **(A)**

- **Other combination therapy for lipid management in diabetic patients** ***(ElSayed et al., 2023k)***
  - Statin plus fibrate combination therapy has not been proven to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **(A)**
  - Statin plus niacin combination therapy has not been proven to improve cardiovascular outcomes over statin medication alone, the combination may raise the risk of stroke with extra adverse effects, and is typically not recommended. **(A)**

Antiplatelet agents in diabetic patients ***(ElSayed et al., 2023k)***

- Aspirin medication (75-162 mg/day) may be considered a primary preventative method in patients with diabetes who are at greater cardiovascular risk after considering the benefit versus the corresponding increased risk of bleeding. **(A)**
  - The use of aspirin in patients under the age of 21 is generally contraindicated due to the risk of Reye syndrome.
  - Aspirin is **not** recommended for persons **at low risk** of ASCVD (such as men and women aged **<50 years** with diabetes and no other major ASCVD risk factors), since the low benefit is likely to be exceeded by the risks of bleeding.
  - Until more research is available, clinical judgment should be used for those at **intermediate risk** (younger patients with one or more risk factors or older patients with no risk factors).
  - Men and women aged **≥ 50 years** with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease) are recommended to use aspirin as primary prevention.
  - For people **>70 years** of age (with or without diabetes), the balance looks to have more risk than benefit. As a result, the use of aspirin for **primary prevention** needs to be carefully considered and may generally **not** be recommended.
- Aspirin therapy (75-162 mg/day) should be used as a secondary preventative approach in diabetics with a history of atherosclerotic cardiovascular disease. **(A)**
- Clopidogrel (75 mg/day) should be administered for diabetic people with atherosclerotic cardiovascular disease and a confirmed aspirin allergy. **(B)**
- The duration of dual antiplatelet therapy with low-dose aspirin and a P2Y12 inhibitor in diabetics following an acute coronary syndrome or acute ischemic stroke/transient ischemic attack should be determined by a multidisciplinary team that includes a cardiovascular or neurological specialist, respectively. **(E)**
- To prevent significant adverse limb and cardiovascular events, persons with stable coronary and/or peripheral artery disease (PAD) and a low bleeding risk might consider combination therapy with aspirin and low-dose rivaroxaban. **(A)**

Specific notes on improvement cardiovascular outcome ***(ElSayed et al., 2023k)***

- To improve cardiovascular outcomes and lower the risk of chronic kidney disease progression in persons with T2DM and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, the addition of finerenone is recommended. **(A)**
- To lower the risk of hospitalization for heart failure in persons with T2DM and diabetic kidney disease, finerenone should be considered. **(A)**
- To lower the risk of cardiovascular events and mortality in diabetic patients with established ASCVD or aged ≥55 years with additional cardiovascular risk factors, ACE inhibitors or ARB medications should be considered. **(A)**
- To lower the risk for progression of asymptomatic stage B heart failure to symptomatic (stage C) heart failure in diabetic patients, ACE inhibitors/ARBs and b-blockers should be considered. **(A)**

Diabetic Foot

Definition

A diabetes-related foot disease includes any infection, ulceration, or tissue loss of a diabetic patient's foot, which can be associated with the presence of peripheral neuropathy, peripheral arterial occlusive disease in the lower extremity, and/or neuro-ostoarthropathy ***(van Netten et al., 2020; van Netten et al., 2023).***

Classification

Table (27) Diabetic Foot Classification adapted from *(Monteiro-Soares et al., 2023; Senneville et al., 2023)*

Clinical Classification of Foot Infection in Patients with Diabetes (IDSA*/IWGDF)**	
Uninfected	Wound lacking suppuration or any local or systemic signs and manifestations of inflammation
Mild infection	Infection present, as defined by the presence of at least 2 of the following criteria **in the absence of any other cause that may induce a local inflammatory response such as trauma, gout, acute Charcot neuro-arthropathy, fracture, thrombosis or venous stasis**: - Local swelling or induration - Erythema > 0.5 to ≤ 2 cm around the ulcer - Local tenderness or pain - Local temperature increase (warmth/hotness) - Purulent discharge (thick, opaque to white, or sanguineous "containing blood" secretion) - Infection is limited to the skin or superficial subcutaneous tissues - Absence of other local complications or systemic illnesses
Moderate infection	Local infection (as above) in a patient who is systemically well and metabolically stable, but which has ≥ 1 of the following characteristics: - Cellulitis extending >2cm - Lymphangitic streaking - Spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone (e.g., fasciitis, septic arthritis, or osteomyelitis)
Severe infection	Infection in a patient with systemic toxicity, Systemic Inflammatory Response Syndrome (SIRS), or metabolic instability (e.g., fever, rigors, hypotension, confusion, vomiting, leucocytosis, acidosis, severe hyperglycemia, or azotemia (increased blood urea nitrogen BUN, ***(Tyagi, 2023)***). Systemic Inflammatory Response Syndrome (SIRS) includes ≥ 2 of the following: - Temperature > 38ºC or < 36ºC - Heart rate > 90 beats/min - Respiratory rate > 20 breaths/min or PaCO2 < 32 mm Hg - White blood cell count > 12,000 or < 4000 cu/mm or 10% immature (band) forms Infection involving bone (osteomyelitis)

*Infectious Diseases Society of America

**International Working Group on Diabetic Foot

Risk Factors ***(Wexler et al., 2024c)***

It's crucial to identify risk factors early and manage them to lower the morbidity of foot ulceration. They include:

- History of foot ulceration
- Neuropathy (loss of protective sensation); which is the most common factor in diabetic foot patient
- Foot deformity
- Vascular insufficiency

Once ulcers form, healing may be challenging, especially if the infection spreads to deep tissues and bone and/or there is reduced local blood flow.

Table (28) Risk Stratification System and Frequency of Foot Screening *by (IWGDF)* adapted from *(Bus et al., 2023)*

Category	Ulcer Risk	Characteristics	Frequency*
0	Very low	No LOPS and no PAD**	Every year
1	Low	LOPS or PAD	Once every 6-12 months
2	Moderate	LOPS + PAD, *or* LOPS + foot deformity *or* PAD + foot deformity	Once every 3-6 months
3	High	LOPS or PAD, and one or more of the following: - history of a foot ulcer - a lower-extremity amputation (minor or major) - end-stage renal disease	Once every 1-3 months

*Screening frequency is based on expert opinion since there is no published evidence to support these intervals.
** LOPS: loss of protective sensation; PAD: peripheral arterial disease.

Prevention ***(Schaper et al., 2023)***

There are five key steps to be considered for the prevention of foot ulcers in diabetic patients:

a. Identification of the at-risk foot
People with a very low risk for ulceration (IWGDF risk category 0) should be screened annually for LOPS and PAD. Asymptomatic presentation of diabetic patients does not rule out foot disease; as they may have asymptomatic neuropathy, peripheral artery disease, pre-ulcerative signs, or even an ulcer.

b. Regular inspection and examination of the at-risk foot (IWGDF risk category 1 or higher): If LOPS or PAD are detected, more frequent screening and more extensive clinical examination and history taking will be needed to aid in management. *Refer to the risk stratification table above for suggested screening frequency.*

***c.* Education of the patient and family.** *See educational material No (7)*

d. Ensuring routine wearing of appropriate footwear

- When choosing or having footwear fitted, people with LOPS or PAD (IWGDF 1-3) must exercise extra caution; this is particularly crucial if they also have foot abnormalities (IWGDF 2) or a history of an ulcer or amputation (IWGDF 3).
- The inside of the shoe shouldn't be too tight or too loose; it should be 1-2 cm longer than the foot. The height should enable space for all the toes, and the internal width should be equivalent to the width of the foot at the metatarsal phalangeal joints (or the widest foot part).


e. Treatment of ulceration risk factors

- Any modifiable risk factor or pre-ulcerative sign on the foot should be treated. This includes removing abundant callus; protecting or draining blisters depending on patients' needs; treating ingrown or thickened nails; and prescribing antifungals for the treatment of fungal infections.
- Proper treatment and control of other risk factors such as hypertension, and hyperglycemia.

Treatment

Treatment of diabetic foot infection

- Do not use systemic or local antibiotics to treat clinically **uninfected foot ulcers** with the intent to minimize the risk of infection or promote the healing of the ulcer ***(Senneville et al., 2023).*** **(Best practice statement)**
- For **mild infection** with low suspicion for resistant organisms (e.g., no recent antibiotic treatment), wound culture is often not required ***(Weintrob et al., 2024).***
- For **moderate or severe infections** and when the concern for multidrug-resistant organisms is high, wound culture is usually useful ***(Weintrob et al., 2024).***
- Ideally, culture samples should be obtained before starting empiric antibiotics. However, antibiotics shouldn't be withheld before obtaining surgical cultures in situations of systemic toxicity or infections that pose a risk to the limb ***(Weintrob et al., 2024).***
- Aspirate from an abscess or curettage from the ulcer base after superficial debridement of necrotic tissue are the preferable clinical specimens for reliable culture. Cultured organisms from superficial swabs are not accurate in identifying the pathogens that cause the deeper infection ***(Weintrob et al., 2024).***
- Wound cultures are usually polymicrobial; while virulent pathogens e.g., Staphylococcus aureus or beta-hemolytic streptococci should be treated, some less virulent isolates e.g., corynebacteria or coagulase-negative staphylococci are frequently contaminants or colonizers and may not require targeted therapy ***(Weintrob et al., 2024).***
- Antibiotics should be initiated parenterally in **severe diabetic foot infections**. Patients may be switched to oral therapy, if available, once there is clinical improvement, given there are no contraindications.
- Antibiotics should be continued in diabetic foot infections for a **duration of 1 to 2 weeks** ***(Senneville et al., 2023).*** **(Strong; High)**
- Consider continuing antibiotics, for up to 3-4 weeks, if the infection is improving but is extensive, or resolving slower than anticipated, or if the patient suffers from severe PAD ***(Senneville et al., 2023).*** **(Conditional; Low)**
- If the infection persists despite having 4 weeks of appropriate treatment, the patient is reassessed and the need for additional diagnostic tests or other treatments is reexamined ***(Senneville et al., 2023).*** **(Strong; Low)**
- **Tigecycline** resulted in lower cure rates and significantly higher rates of adverse events ***(Senneville et al., 2023).***
- Consider continuing antibiotics, for up to 3-4 weeks, if the infection is improving but is extensive, or resolving slower than anticipated, or the patient suffers from severe PAD ***(Senneville et al., 2023).*** **(Conditional; Low)**
- If the infection persists despite having 4 weeks of appropriate treatment, the patient is reassessed and the need for additional diagnostic tests or other treatments is reexamined ***(Senneville et al., 2023).*** **(Strong; Low)**

Table (29) Potential Empiric Therapy for the Treatment of Diabetic Foot Infections ***(Senneville et al., 2023; Weintrob et al., 2024)***

Infection Severity	Probable Pathogen(s)	Antibiotic Regimen
Mild	MSSA, Streptococcus spp.	- Cephalexin PO - Amoxicillin/clavulanate PO - Clindamycin PO - Levofloxacin PO
	MRSA§	- Clindamycin - Trimethoprim-sulfamethoxazole - Doxycycline (in combination with cephalexin in case of suspected streptococci)
Moderate or Severe	MSSA, Streptococcus spp., Enterobacteriaceae, anaerobes	- Amoxicillin/clavulanate - Ampicillin/sulbactam IV - Cefoxitin - Ceftriaxone + metronidazole - Ertapenem - Meropenem - Imipenem/Cilastatin - Levofloxacin - Moxifloxacin - Clindamycin
	Pseudomonas aeruginosa∞	- Aztreonam - Cefepime - Ceftazidime - Piperacillin/tazobactam - Imipenem/Cilastatin - Meropenem
	MRSA§	- Vancomycin - Teicoplanin - Linezolid - Daptomycin
	MRSA§, Enterobacteriaceae, P. aeruginosa∞, anaerobes	- Vancomycin, Teicoplanin, Linezolid or Daptomycin **PLUS** - Antipseudomonal β-lactam ± Metronidazole

*MSSA (Methicillin-Susceptible Staphylococcus Aureus) **MRSA (Methicillin Resistant Staphylococcus Aureus)

§ ***MRSA Risk Factors that should prompt the addition of anti-MRSA to the empirical regimen*** ***(Senneville et al., 2023; Weintrob et al., 2024)***

- Prior prolonged, inappropriate, or recent antibiotic use
- Prolonged or recent hospitalization, intensive care admission
- The long duration of the foot wound
- The presence of osteomyelitis
- Prior MRSA infection or colonization within the past year
- The local prevalence of MRSA is high enough (perhaps 50% for a mild and 30% for a moderate soft tissue infection)
- Severe infection, and open wounds

- Invasive procedures
- HIV infection
- Admission to nursing homes
- Haemodialysis
- Discharge with long-term central venous access

∞ ***P. aeruginosa risk factors that should prompt the addition of anti-P.aeruginosa to the empirical regimen (Senneville et al., 2023; Weintrob et al., 2024)***

- Patients having severe infection
- High local prevalence of Pseudomonas infection
- Warm climate
- Frequent exposure of the foot to water

Mouth problems

- Gum disease, also known as periodontal gum disease, is the most prevalent and significant mouth condition associated with diabetes. Untreated, the condition progresses in stages, from inflamed gums ("gingivitis") to periodontitis and tooth loss ***(NIDDK, 2022).***
- Diabetes, in addition to increasing the risk of gum disease, also raises the risk of the following ***(NIDDK, 2022):***
  - Dental cavities.
  - Dry mouth, a lack of saliva that can lead to sores, ulcers, and infections.
  - Thrush which is a fungal infection that causes painful, white spots in the mouth.
  - Burning mouth syndrome which is a burning feeling within the mouth produced by excessive blood glucose levels
  - Alterations in the taste of meals and beverages
- These dental issues, as well as tooth loss, might make it difficult to stick to a healthy eating plan that can help the patient control -his/her diabetes ***(NIDDK, 2022).***
- The presence of gum disease may make it more difficult to control blood glucose, as gums become inflamed and inflammation in the body can lead to higher blood glucose levels—which can contribute to a higher risk of diabetes development and uncontrolled diabetes. So, people with uncontrolled diabetes who are treated for gum disease will have lower blood sugar levels over time ***(ADA, 2023; CDC, 2023; CDC, 2024).***

Causes

- Uncontrolled diabetes causes and raises the likelihood of mouth problems, causing them to worsen from mild to severe ***(NIDDK, 2022).***

Signs and Symptoms ***(ADA, 2023; CDC, 2023; CDC, 2024; NIDCR, 2023; NIDDK, 2022)*****:** *See educational material No (9)*

Prevention

- Education regarding warning signs and symptoms of gum disease should be provided to minimize complications and potentially save money in the long term ***(ADA, 2023).***
- Check regularly and contact the dentist if the dentures do not fit right, or if gums are sore ***(NIDCR, 2023).***
- **For further information,** *see educational material No (9)* ***(ADA, 2023; CDC, 2023; CDC, 2024; NIDCR, 2023; NIDDK, 2022).***

Treatment

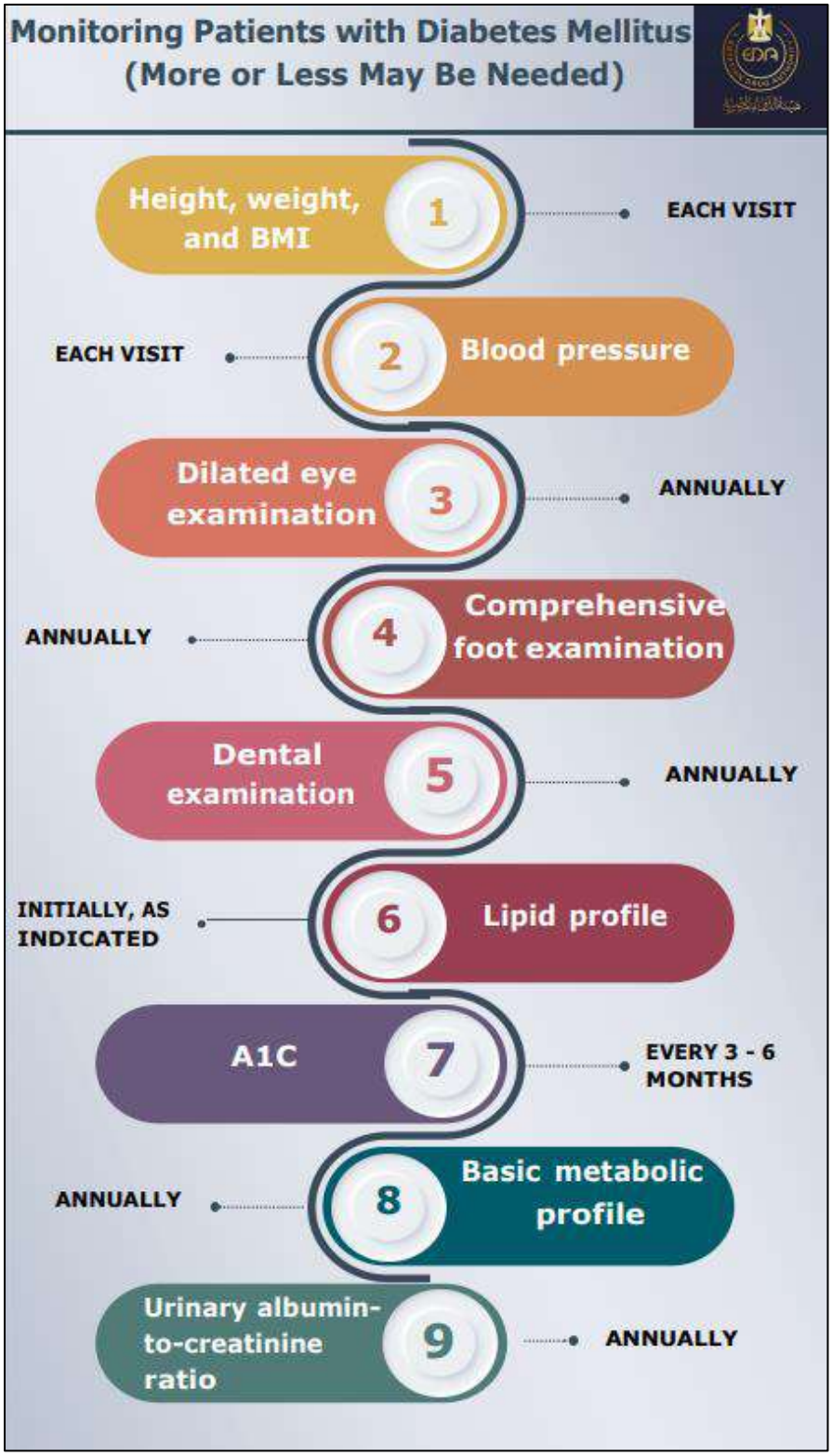
- Control diabetes as it can delay healing, which might make periodontal disease treatment more difficult ***(ADA, 2023; NIDCR, 2023).***
- Treatment based on which problem is present:
  - *People with periodontal disease:* Deep cleaning of the teeth or referral for gum surgery is recommended. A specific mouth rinse may also be prescribed by the dentist ***(NIDCR, 2023).***
  - *To treat symptoms of thrush:* The dentist may prescribe antifungal and a special solution to clean dentures (false teeth) ***(NIDCR, 2023).***
  - *For dry mouth*: A dentist may prescribe medication to keep the mouth moist ***(NIDCR, 2023).***

ANNEXES

Annexes

Pharmacist Educational Materials

1) Monitoring Patients with Diabetes Mellitus



2) Education and Counseling Tips for Diabetic Patients

3) High Risk Groups for Developing Diabetes

4) Injectable Diabetic Medications

5) Insulin Administration

Insulin Strength

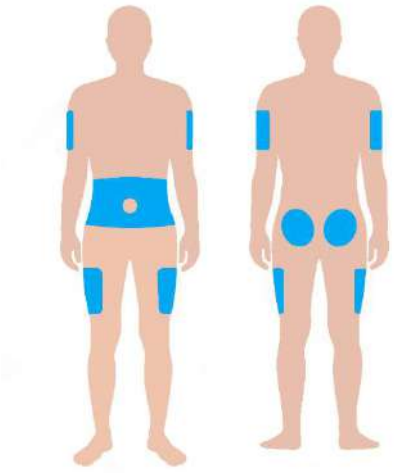
Most insulin preparations come in a strength of 100 units per milliliter (U-100); however, less or more concentrated preparations of insulin are available:

- Less concentrated forms of insulin like U-40 insulin.
- More concentrated forms of insulin like U-200 and U-300 insulin are used to give high doses of insulin in smaller injection volumes, which is beneficial for patients who are extremely resistant to insulin and require very large doses ***(American Diabetes Association, 2003)***.

To deliver an insulin dose accurately, it is important to check the concentration of insulin and use a syringe with a grading that matches the concentration.

Injection Sites ***(American Diabetes Association, 2003)***

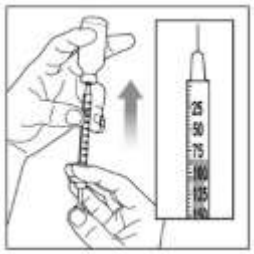
Insulin should be injected into the subcutaneous tissue of the upper arm, anterior and lateral surfaces of the thigh, the buttocks, and the abdomen, 5 cm away from the navel ***(American Diabetes Association, 2003)***. The rate of insulin absorption varies from different injection sites: it is fastest in the abdomen, followed by the upper arms, then the thighs. Repeated injections in the same spot cause lipodystrophy; absorption from areas with lipodystrophy is slow and erratic which necessitates rotation of the injection site.

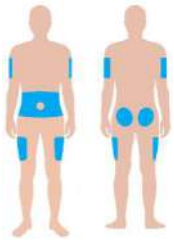


Insulin Syringes

1. Preparation	
1.1. Wash hands thoroughly with soap and water.	
1.2. Get the required equipment: syringe, insulin vials, alcohol wipes, and a waste disposal container.	
1.3. Check the label and verify the correct type of insulin is used.	
1.4. Check the insulin vial closely: • Almost all insulin preparations are clear and colorless. • Only preparations that contain NPH: intermediate-acting insulin and premixed insulin, are cloudy.	

1.5. Verify that the grading on the syringe matches the concentration of the insulin preparation. **Using U-100 syringes for U-200 or U-300 insulin puts the patient at risk of receiving an overdose!**	 *U-100 Insulin Syringe*
1.6. If the vial was in the refrigerator, leave it to reach room temperature.	
2. Filling the syringe	
2.1. If the vial is new, remove its cap.	
2.2. Wipe the rubber stopper with an alcohol swab.	
2.3. Remove the syringe's cap and pull the plunger to draw as much air into the syringe as the volume of the dose.	

2.4. For all types of insulin, except for short and rapid-acting insulin and insulin glargine, roll the vial in the palms of the hand gently to re-suspend the insulin. **Do not shake the vial.**	
2.5. Inject the syringe's needle through the vial's rubber stopper and press the plunger to inject all the air into the vial.	 
2.6. With the syringe injected into the vial, hold the vial and the syringe in an inverted position, and with the tip of the syringe's needle under the surface of the insulin solution inside the vial, start pulling the plunger down slowly until the tip of the plunger is a few units past the dose.	
2.7. Before pulling the syringe out of the vial, inspect the syringe carefully for air bubbles. In case the syringe has bubbles:	
2.7.1. Tap the syringe body gently to release any bubbles to the top.	
2.7.2. Gently press the plunger so that any air trapped on top of the solution is returned to the vial until the tip of the plunger is exactly at the line of the dose.	

2.8. Pull the syringe out of the vial, and set the syringe aside making sure the needle does not touch anything.	
3. Injection procedure	
3.1. Select an injection site.	
3.2. Wipe the selected area with an alcohol swab, and wait for the alcohol on the skin to dry completely before injection.	
3.3. Insert the whole needle under the skin at a 90° angle. In pediatric patients and patients with thin subcutaneous tissue, injecting at a 45° angle might be better to avoid intramuscular injection.	
3.4. Press the plunger to inject the dose, verify the injection is complete, and leave the needle inside the skin for 5 seconds.	

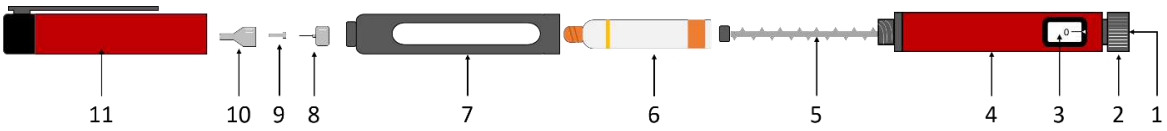
3.5. Withdraw the needle out of the skin at the same insertion angle. If pain occurs after the injection, or if bleeding occurs, apply gentle pressure to the injection site for 5 seconds without rubbing.	

4. Waste disposal
   The syringe and all the tools used should be placed in a safety container.
   Putting the cap of the syringe back on may result in needle injuries and, thus, should be avoided.

Insulin Pens

Disclaimer: *The following illustrations and instructions are intended to give a general outline of the components of insulin pens and use instructions; however, pens available in the market might vary in terms of their components, injection mechanisms, needle compatibility, and use instructions. For detailed information, always refer to the manufacturer's user guide for the pen device and the manufacturer's labeling for the insulin type used.*

Reusable Insulin Pens

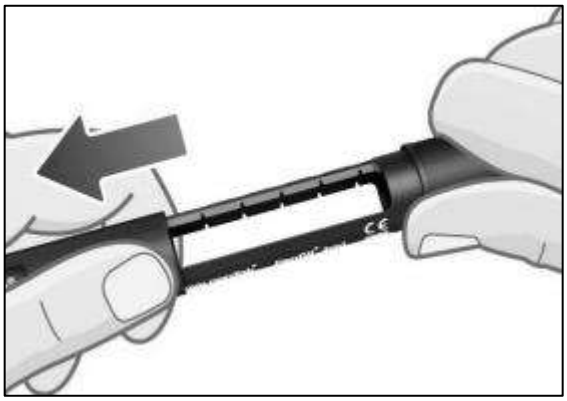
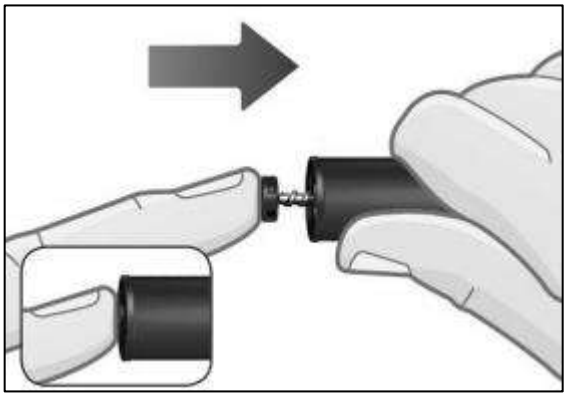


Reusable Insulin Pen

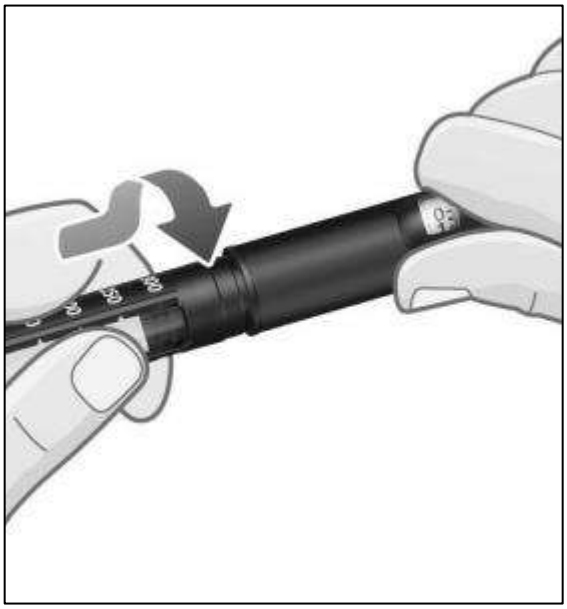
Insulin pen parts:

1. Injection button: pressed to inject a dose.
2. Dose knob: rotated to set the dose.
3. Dose window shows the dose as the knob is rotated.
4. Pen body
5. Piston rod: pushes insulin out of the cartridge through the needle
6. Insulin cartridge
7. Cartridge holder
8. Needle
9. Needle inner shield.
10. Needle outer shield.
11. Pen cap

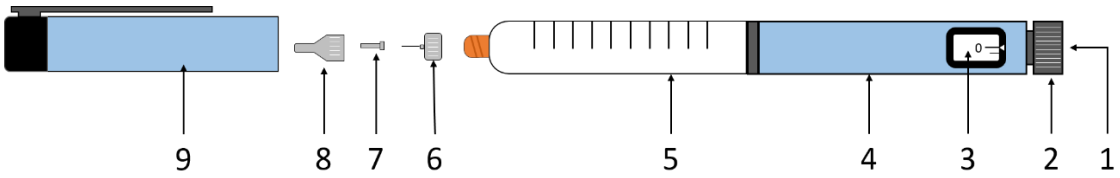
Procedure for installing cartridges:

1. Remove the pen cap.	
2. Unscrew the cartridge holder to detach it from the pen body.	
3. Apply slight pressure to the tip of the piston rod to reset its position.	

4. If the cartridge holder had an empty cartridge inside, let the cartridge slide out.	
5. Inspect the new insulin cartridge: • Verify the type of insulin and its concentration. • Inspect the cartridge for any damage. • Inspect the insulin solution inside the cartridge. The insulin solution should be colorless and clear unless it has an NPH component as mentioned above.	
6. Slide the new cartridge into the cartridge holder so that the rubber stopper of the cartridge goes in first.	

7. Screw the cartridge holder back to the pen body. Keep screwing until the holder clicks.	

Disposable Insulin Pens

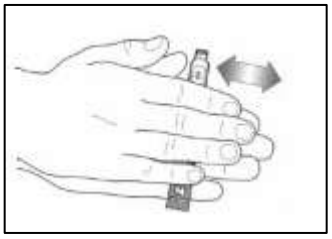
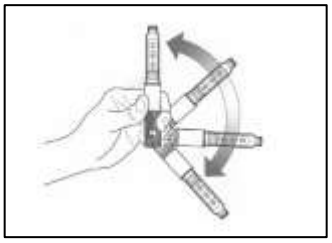
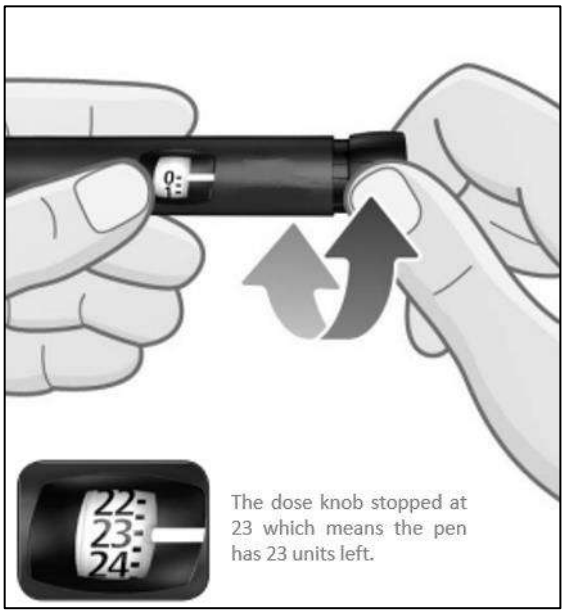


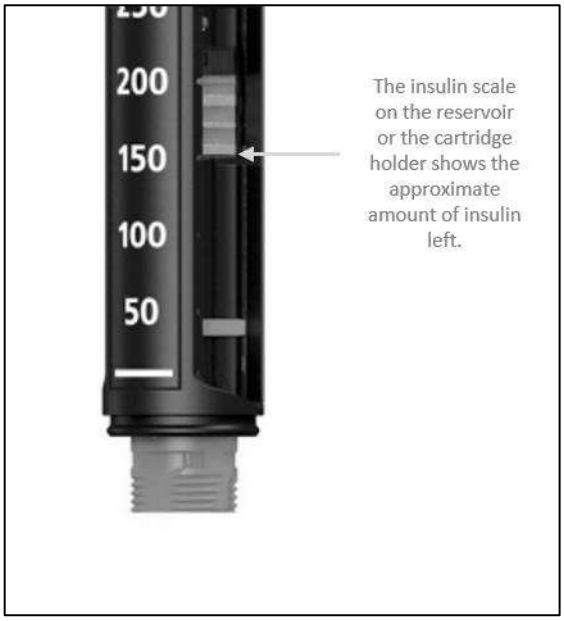
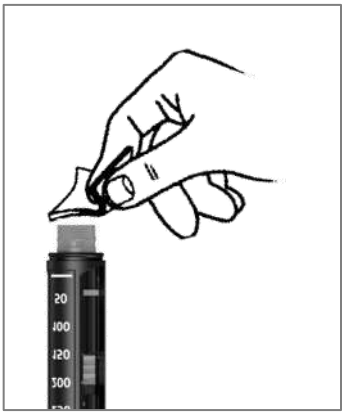
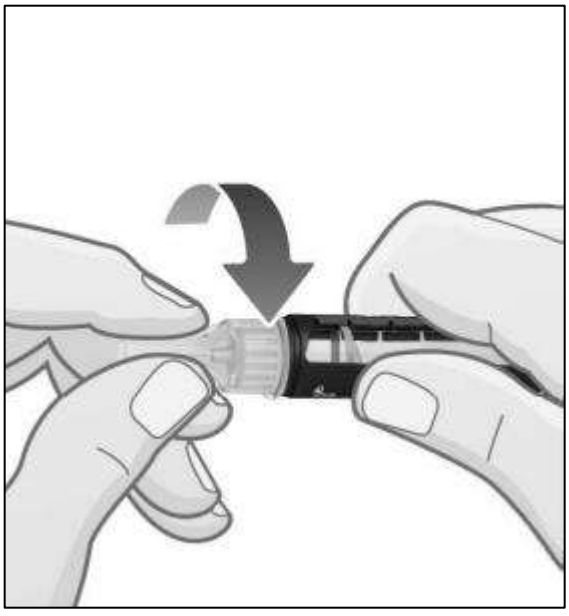
Disposable Insulin Pen

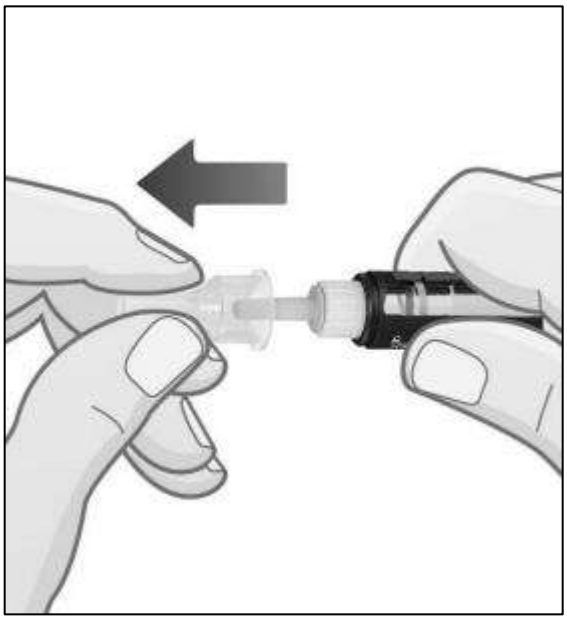
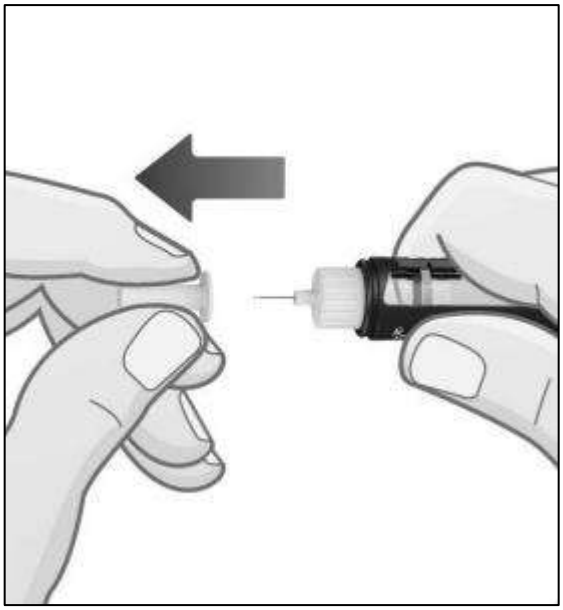
Insulin pen parts:

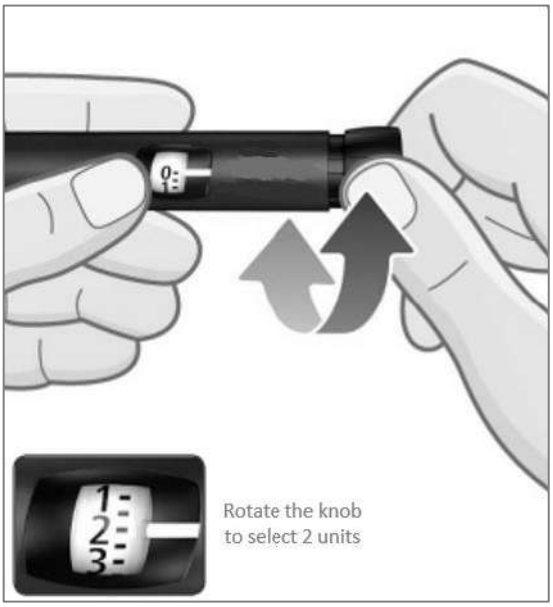
1. Injection button: pressed to inject a dose.
2. Dose knob: rotated to set the dose.
3. Dose window: shows the dose as the knob is rotated.
4. Pen body
5. Insulin reservoir: disposable insulin pens have insulin reservoirs that are un-detachable from the pen body, contrary to cartridges and cartridge holders of reusable pens. When the reservoir has run out of insulin, the whole pen is discarded.
6. Needle
7. Needle inner shield.
8. Needle outer shield.
9. Pen cap

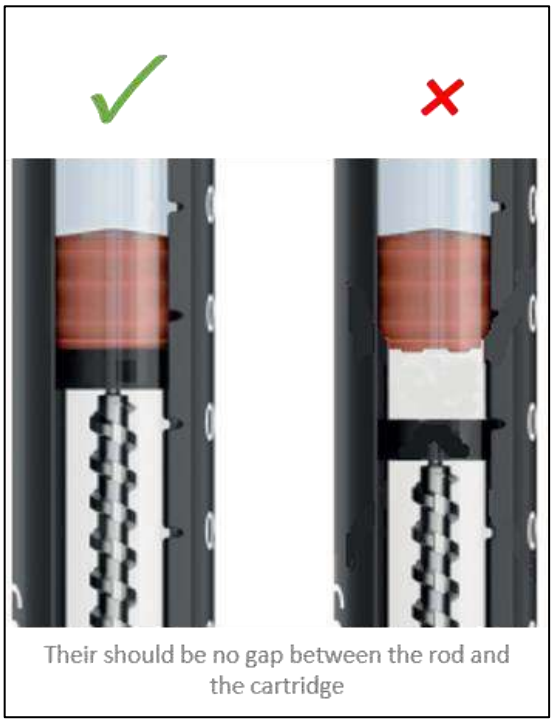
Injecting Insulin with Pens

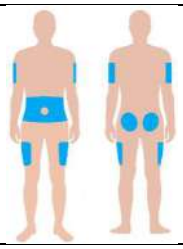
<table>
<tr><td colspan="2">1. Suspend insulin: insulin products containing insulin NPH should be suspended just before use.</td></tr>
<tr><td>1.1. Roll the pen between the palms of your hand gently 10 times.</td><td>  </td></tr>
<tr><td>1.2. Invert the pen up and down gently 10 times.</td><td>  </td></tr>
<tr><td colspan="2">2. If the pen or the cartridge is in the refrigerator, leave it to reach room temperature.</td></tr>
<tr><td colspan="2">3. Check the amount of insulin left in the pen
The amount of insulin left in the pen can be checked in two ways:</td></tr>
<tr><td>3.1. Rotate the dose knob; the knob will keep rotating until either:</td><td></td></tr>
<tr><td>• The dose shown on the dose window is equal to the amount of insulin remaining.</td><td> 
</td></tr>
<tr><td>• The maximum dose is reached. The maximum dose varies between pen devices; pen devices deliver max doses of 30 – 120 units.</td><td></td></tr>
</table>

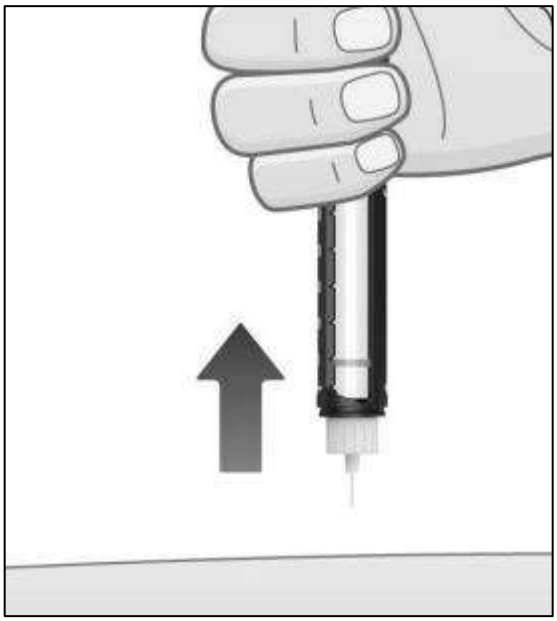
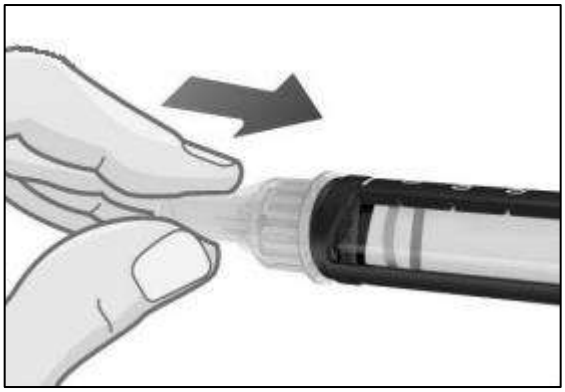
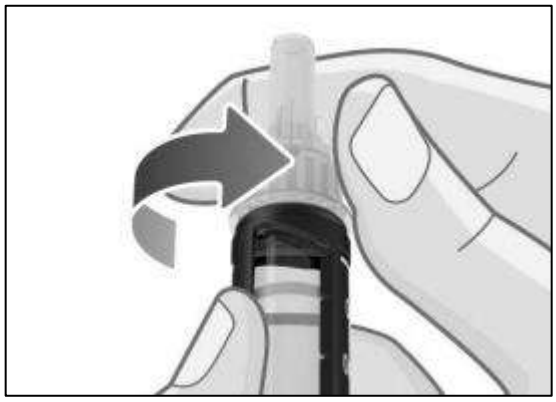
3.2. The insulin scale on the reservoir/cartridge holder shows the approximate amount of insulin left in the pen.	
4. Attach a needle	
4.1. Wipe the rubber stopper of the reservoir/cartridge with an alcohol swab.	
4.2. Remove the paper cover from the bottom of the needle, push the needle into the rubber stopper of the cartridge/insulin reservoir, and screw until the needle is tightly fixed.	

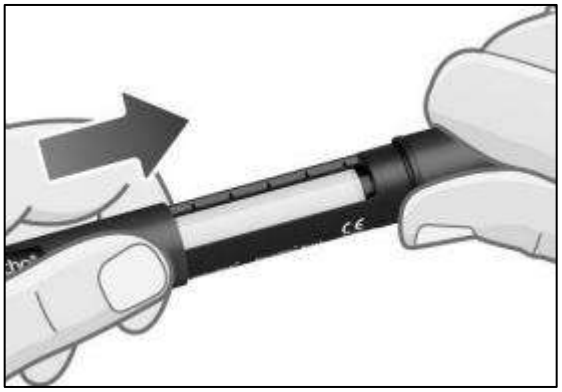
4.3. Remove the outer needle shield.	
4.4. Remove the inner needle shield.	
5. Injection procedure	
5.1. Prime the pen Air may be introduced into the insulin reservoir/cartridge during the manufacturing process, and if needles are left attached to the pen for a long time in between injections. Before using the pen, it should be primed with 2 units to verify the flow of insulin out of the needle. The presence of air bubbles in the reservoir/cartridge might affect the accuracy of the dose.	

5.1.1. Rotate the dose knob until the dose window shows 2.	
5.1.2. Hold the pen with the needle pointing up and tap the insulin reservoir/cartridge gently to release any air bubbles to the top.	

5.1.3. Press the injection button until the dose window shows zero. Insulin should come out from the needle.	
5.1.4. If insulin does not come out of the needle: • Verify there is no gap between the piston rod and the cartridge (reusable pens only). • The needle might be clogged especially if it was used multiple times. • The device might be broken, in which case, contact the manufacturer for support. Otherwise, keep repeating steps 5.1.1 to 5.1.3 until all the trapped air has been expelled and insulin comes out of the needle.	

5.2. Rotate the dose knob to select the dose. Make sure the dose pointer is aligned with the dose.	
5.3. Select injection site.	
5.4. Wipe the injection site with an alcohol swab.	
5.5. Insert the whole needle under the skin at a 90° angle, press the button until the dose window shows zero, and wait for 5 seconds before pulling the needle out.	

5.6. Pull the pen out at the same insertion angle.	
6. Waste disposal	
6.1. Carefully put the outer needle shield back on the needle. Do not attempt to put the inner shield back on the needle; this might cause an injury.	
6.2. Hold the cartridge holder/reservoir with one hand and use the other to unscrew the needle and detach it from the pen.	
6.3. Use a safety container for waste disposal (needles, cartridges, swabs, etc.)	

6.4. Put the pen cap on.	

Insulin Pumps

Insulin pumps deliver rapid-acting insulin throughout the day by continuous subcutaneous infusion to maintain blood glucose levels within target ranges.

A meta-analysis concluded that the use of insulin pumps offers modest advantages over multiple daily injections (MDI) in terms of reducing A1C (- 0.3%, 95% CI: - 0.58 to - 0.02), and reducing hypoglycemia in adults and children ***(ElSayed et al., 2022)***. No consensus guides the choice between pumps and MDI; the choice should be based on individual patient characteristics and preferences.

Typical insulin pumps consist of an insulin reservoir held within the pump's main body that is connected to an infusion set by a tube and software that controls insulin delivery and allows users to interact with the pump. Later innovations aimed at overcoming the inconvenience of tubes and infusion sets led to the introduction of patch pumps; patch pumps are directly attached to the body without tubes and infusion sets which allows users to be more comfortable while performing routine and physical activities ***(Kesavadev et al., 2020)***.

Early insulin pumps were not fully automated; they required users to input parameters like insulin to carb ratio, amount of carbohydrates in a meal, etc., and to manually adjust the rate of basal insulin. In addition, earlier pumps did not adjust their infusion rates in response to blood glucose levels which posed a risk of hypoglycemia.

Modern pumps incorporate features like linking the pump to blood glucose measurement devices and smart devices (sensory-augmented pumps or SAP), suspending insulin infusion in response to low blood glucose levels (threshold suspension), more advanced computer algorithms for control of insulin delivery, and minimizing user input. Modern pumps linked to continuous glucose monitoring devices can automatically adjust basal insulin every few minutes, and automatically administer corrective bolus insulin.

Comparison Between Syringes, Pens, and Pumps ***(Kesavadev et al., 2020)***

	Advantages	Disadvantages
Syringes	• Cheap • Widely available	• Poor dose accuracy • Difficult to use. • Inconvenient to use in public. • Multiple daily injections. • Injection can be painful compared to pens.
Pens	• Convenient, especially for use in public. • Accurate dosing. • Easy to use. • Cost-effective compared to pumps.	• The acquisition cost of the pen can be high. • No capacity for insulin mixing. Only premixed formulations can be used. • The maximum dose that can be given by a pen is low (60 – 120 units). • Multiple daily injections.
Pumps	• Better glycemic control: insulin is infused from a single site for a long period which eliminates variability from changing injection sites due to changes in the thickness of the subcutaneous tissue. • The injection site needs to be changed once every 2 – 3 days. • More flexible.	• Inconvenience from tubes and infusion sets that can be dislodged or clogged. • Very high acquisition cost. • Require patients to better understand important diabetes concepts like insulin-to-carb ratio so they can adjust their pumps. • Skin reactions from prolonged attachment and insulin infusion from the same site like irritation, lipohypertrophy, or lipoatrophy.

6) Oral Diabetic Medications

Patient Educational Materials

7) Diabetic Foot

8) Diabetes Symptoms

الالتهابات المتكررة في الجلد	
بطء التئام الجروح	
زغللة بالعين وعدم وضوح الرؤية	
وخز أو تنميل في اليدين والقدمين	

9) Teeth and Gums in Diabetes

10) Hyperglycemia

العوامل التي تزيد منها

- وجود عدوى
- عدم أخذ الأنسولين بانتظام (في حالة وصفه)
- جرعات غير مناسبة من الأدوية
- تناول بعض الأدوية التي تزيد من مستوى السكر مثل الكورتيزون

الأعراض

- كثرة التبول
- كثرة العطش
- الإحساس بالضعف
- التغير في حالة الإدراك والحالة العقلية
- وجود رائحة الفواكه في النفس
- وجود علامات الجفاف
- فقدان الوعي وغيبوبة في الحالات الشديدة

الإسعافات الأولية وكيفية التعامل في وجود أي مرض حاد

الإسعافات الأولية:

- في حالة عدم أخذ جرعات أي أدوية يجب تناولها في الحال.
- في حالة عدم انخفاض السكر للمعدلات الطبيعية أو تطور الحالة يجب الانتقال إلى المستشفى.
- تعليم المريض كيفية استعمال شرائط قياس السكر أو الكيتون المنزلية، للتعرف المبكر على ارتفاع السكر الكيتوني.

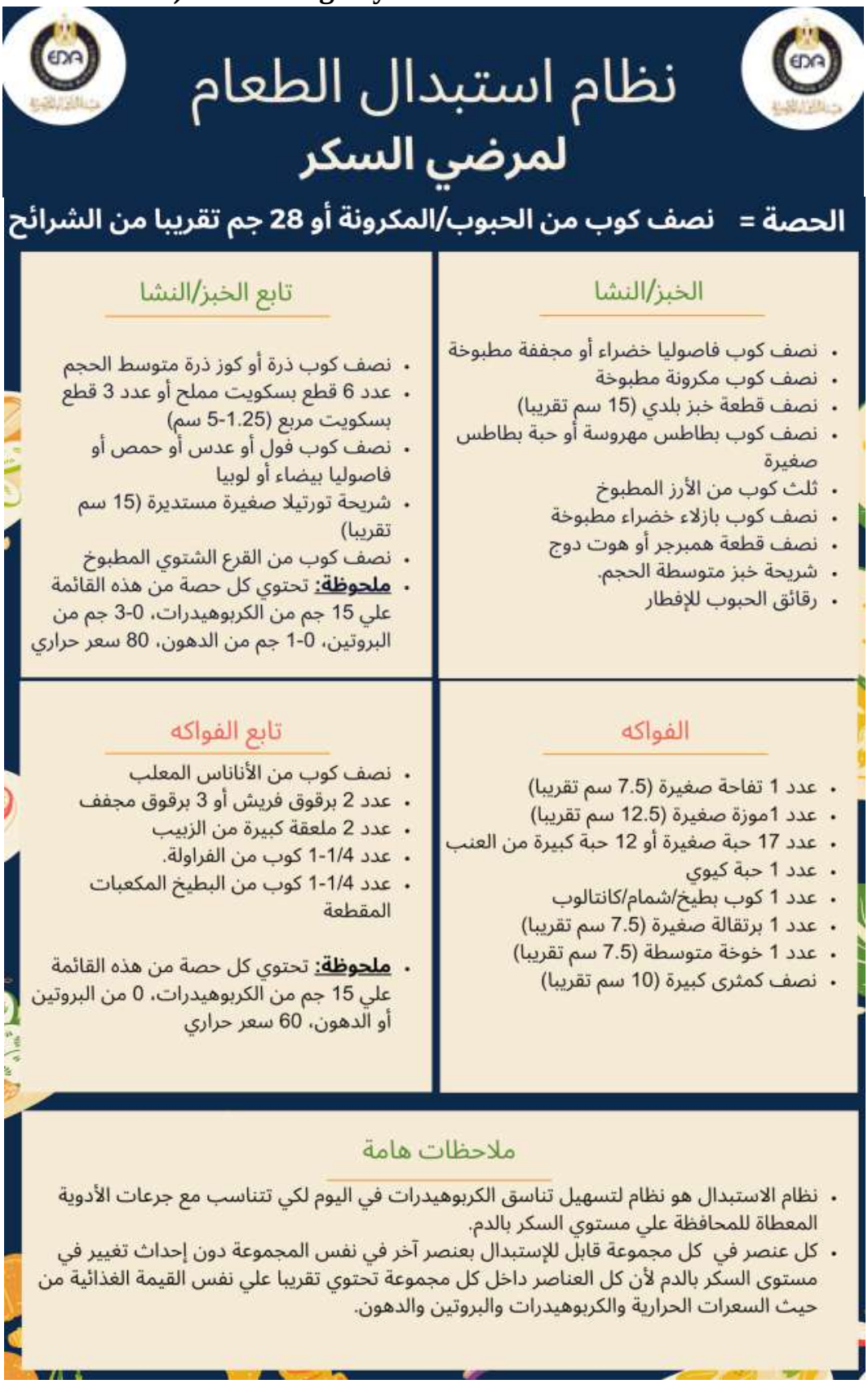
كيفية التعامل في وجود أي مرض حاد

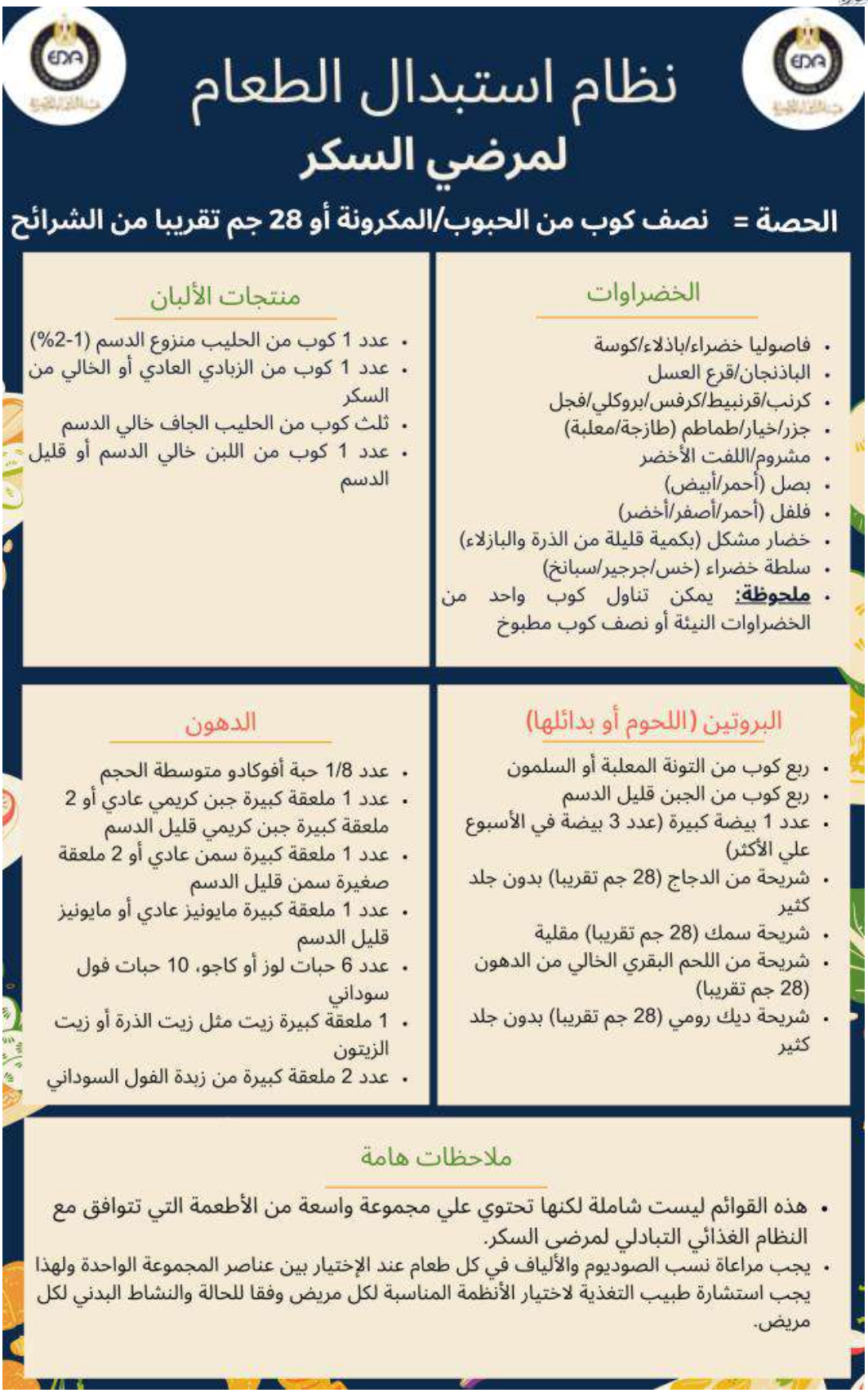
- يجب قياس درجة الحرارة باستمرار مع استخدام خافضات حرارة.
- يجب أخذ أدوية السكر بانتظام وخاصة الأنسولين مع متابعة مستوى السكر بالدم.
- تثقيف المريض للحصول على نظام غذائي سائل سهل الهضم يحتوي على الكربوهيدرات والملح عند الشعور بالغثيان لمنع غيبوبة ارتفاع السكر.

11) Instruction on Controlling Blood Glucose Level and Prevention of Diabetes Complications

12) General Counselling Points for Diabetic Patients in Ramadan

13) Exchange System for Diabetic Patients




نظام استبدال الطعام
لمرضي السكر
الحصة = نصف كوب من الحبوب/المكرونة أو 28 جم تقريبا من الشرائح
الخضراوات
فاصوليا خضراء/باذلاء/كوسة
الباذنجان/قرع العسل
كرنب/قرنبيط/كرفس/بروكلي/فجل
جزر/خيار/طماطم (طازجة/معلبة)
مشروم/اللفت الأخضر
بصل (أحمر/أبيض)
فلفل (أحمر/أصفر/أخضر)
خضار مشكل (بكمية قليلة من الذرة والبازلاء)
سلطة خضراء (خس/جرجير/سبانخ)
ملحوظة: يمكن تناول كوب واحد من الخضراوات النيئة أو نصف كوب مطبوخ
منتجات الألبان
عدد 1 كوب من الحليب منزوع الدسم (1-2%)
عدد 1 كوب من الزبادي العادي أو الخالي من السكر
ثلث كوب من الحليب الجاف خالي الدسم
عدد 1 كوب من اللبن خالي الدسم أو قليل الدسم
البروتين (اللحوم أو بدائلها)
ربع كوب من التونة المعلبة أو السلمون
ربع كوب من الجبن قليل الدسم
عدد 1 بيضة كبيرة (عدد 3 بيضة في الأسبوع علي الأكثر)
شريحة من الدجاج (28 جم تقريبا) بدون جلد كثير
شريحة سمك (28 جم تقريبا) مقلية
شريحة من اللحم البقري الخالي من الدهون (28 جم تقريبا)
شريحة ديك رومي (28 جم تقريبا) بدون جلد كثير
الدهون
عدد 1/8 حبة أفوكادو متوسطة الحجم
عدد 1 ملعقة كبيرة جبن كريمي عادي أو 2 ملعقة كبيرة جبن كريمي قليل الدسم
عدد 1 ملعقة كبيرة سمن عادي أو 2 ملعقة صغيرة سمن قليل الدسم
عدد 1 ملعقة كبيرة مايونيز عادي أو مايونيز قليل الدسم
عدد 6 حبات لوز أو كاجو، 10 حبات فول سوداني
1 ملعقة كبيرة زيت مثل زيت الذرة أو زيت الزيتون
عدد 2 ملعقة كبيرة من زبدة الفول السوداني
ملاحظات هامة
هذه القوائم ليست شاملة لكنها تحتوي علي مجموعة واسعة من الأطعمة التي تتوافق مع النظام الغذائي التبادلي لمرضى السكر.
يجب مراعاة نسب الصوديوم والألياف في كل طعام عند الإختيار بين عناصر المجموعة الواحدة ولهذا يجب استشارة طبيب التغذية لاختيار الأنظمة المناسبة لكل مريض وفقا للحالة والنشاط البدني لكل مريض.

14) Hypoglycemia

العوامل التي تزيد منها

- زيادة ممارسة الرياضة
- الصيام لفترات طويلة
- وجود أخطاء دوائية أثناء استخدام الأنسولين
- تناول جرعات أدوية غير مناسبة

Hypoglycemia

الأعراض

- زيادة ضربات القلب
- الرعشة
- القلق
- التعرق
- الإحساس بالجوع

- تنميل
- الإحساس بالضعف والميل إلى النوم
- دوخة والهذيان والارتباك
- في الحالات الشديدة قد تصل لتشنجات وغيبوبة

- يجب بدء العلاج في الحال لإن استمرار هبوط السكر لفترة يؤدي إلى موت خلايا المخ.
- في حالة الشك في معرفة نوع الغيبوبة (هبوط أو ارتفاع السكر)، يجب التعامل مع الحالة على إنها هبوط سكر لأنها أخطر على المخ.
- يتم أخذ 150-200 مللي عصير فاكهه مثل عصير البرتقال، أو 3-4 ملاعق سكر+ ماء (لكنه لا يكون مفيد في حالة تناول المريض دواء acarbose)، ثم يتم قياس السكر بالدم بعد 15 دقيقة. لو استمر السكر أقل من 70 مجم / ديسيلتر تعاد الخطوات السابقة 3 مرات.
- في حالة عدم الاستجابة يجب نقل المريض إلى المستشفى على الفور.

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