

**National Guideline for Management of
Diabetes**

For Secondary and Tertiary healthcare level



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Directorate of Non-Communicable Diseases
Ministry of Health

National Guideline for Management of Diabetes

For Secondary and Tertiary care guideline

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to serve as a reference to the doctors managing this common condition at secondary and tertiary healthcare level.

This document was reviewed by the Directorate of NCD to be in line with the National policies, strategies and regulations.

Feedback of relevant professional colleges and institution was also incorporated into this guideline

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Table of contents

Contents

List of figures	xi
List of Annexures	xii
Abbreviations.....	xiii
Introduction	1
Methodology and review.....	1
Intended Use	2
Chapter 1.....	3
1.1 Introduction and epidemiology	3
1.2 Pathogenesis of diabetes	3
1.3 Diabetes related complications.....	4
1.4 History of diabetes	4
1.5 Global epidemiology	4
Chapter 2	7
Diagnosis	7
2.1 Diagnostic tests	7
2.1.1 FPG, 2-h PG during 75-g OGTT, random plasma glucose	9
2.1.2 HbA1c	9
2.1.3 Random plasma glucose can be used for diagnosis	10
2.2 Confirming the diagnosis of diabetes.....	11
2.3 Diagnosis of diabetes in pregnancy	11
2.4 Aetiological diagnosis of diabetes.....	11
Chapter 3.....	12
Classification of Diabetes	12
3.1. Introduction	12
3.2. Types of diabetes.....	12
3.3. A practical method of assigning diabetes type in clinical settings.....	13
3.3.1 Steps in clinical subtyping when an individual first diagnosed with diabetes.....	13
3.4. Type 1 Diabetes (T1DM).....	13
3.4. Type 2 Diabetes (T2DM).....	15
3.5. Hybrid forms of DM	15
3.5.1. Slowly evolving immune-mediated diabetes.....	15
3.5.2. Ketosis prone T2DM	16
3.6. Hyperglycemia first detected in pregnancy.....	17

3.7. Other specific types of diabetes	17
3.7.1. Monogenic diabetes	17
3.7.2. Diseases of the exocrine pancreas.....	19
3.7.3. Endocrine disorders.....	19
3.7.4. Drug or chemical-induced diabetes.....	19
3.7.5. Infection-related diabetes.....	21
3.7.6. Uncommon specific forms of immune-mediated diabetes	21
3.7.7. Other genetic syndromes sometimes associated with diabetes.....	21
3.8. Unclassified Diabetes	21
Chapter 4.....	22
Prediabetes	22
4.1. Introduction	22
4.2. Diagnosis.....	22
4.3. Cardiovascular risk	22
4.4. Management of Prediabetes	22
Chapter 5.....	23
Clinical and laboratory evaluation of disease progression, complications and assessment of glycemic control	23
5.1. General Recommendations.....	23
5.2. Recommendations for HbA1c Testing	23
5.3. Monitoring for glycemic control/ development of complications.....	24
5.4. Cardiovascular Disease.....	25
5.5. Erectile Dysfunction	25
5.6. Chronic Kidney Disease.....	25
5.7. Diabetic Retinopathy.....	25
5.8. Neuropathy.....	25
5.9. Foot screening.....	25
Recommendations for screening refer to chapter 13.....	25
Chapter 6.....	26
Management of type 2 diabetes	26
6.1 Introduction.....	26
6.1.1 EVALUATION	27
6.1.2 TREATMENT TARGETS AND DETERMINANTS	28
6.1.3. PLAN OF MANAGEMENT	31
6.1.4. REVIEW	31
6.2. Pharmacological interventions for diabetes management	31

6.3 Insulin therapy.....	35
6.4 Diabetes remission	39
Chapter 7.....	40
Management of Type 1 Diabetes Mellitus	40
7.1. Introduction	40
7.2. Diagnosis.....	40
7.3. Immediate Management	42
7.4. Early Care Plan.....	42
7.4.1. Early care plan for patients with T1DM should include:.....	42
7.5. Blood glucose monitoring and glycemic goals.....	42
7.5.1. HbA1c measurement	42
7.5.2. Self-Monitoring of Blood Glucose (SMBG)	42
7.6. Treatment	43
7.6.1. Insulin regime.....	43
7.6.2. Long-acting insulin	43
7.6.3. Short/Rapid acting insulin	43
7.6.4. Pre-mixed insulin	44
7.6.5. Adjuncts	44
7.7. Transitional care in T1DM.....	44
7.8. Follow-up consultations and long-term care	45
Chapter 8.....	46
MANAGEMENT OF DIABETES SECONDARY TO PANCREATITIS	46
8.1 Introduction.....	46
8.1.1 Screening for pancreatogenic diabetes.....	46
8.1.2 Diagnosis of pancreatogenic diabetes.....	46
8.1.3 Management of pancreatogenic diabetes	46
8.2 STEROID INDUCED DIABETES	47
8.2.1 Introduction	47
8.2.2. Patients with no known Diabetes	47
8.2.3 Guidance for patients with T2DM on Steroid therapy	49
8.2.4 Hospital discharge of patients at high risk of steroid induced diabetes/ hyperglycaemia	49
Chapter 9.....	51
Insulin	51
9.1. Introduction	51
9.2. Types of insulins available:	51

9.3. Insulin regimens	53
9.3.1. Basal only insulin regimens.....	54
9.3.2. Basal plus regimen	54
9.3.3. Split mixed /pre-mixed insulin regimens	54
9.3.4. Premixed plus	55
9.3.5. Basal bolus insulin regimens.....	55
9.4. Titrating the dose of insulin.....	55
9.5. Common Adverse effects.....	56
9.6. Biosimilar Insulins (BIs)	56
Chapter 10.....	57
Non-insulin anti-diabetics – oral and injectable.....	57
10.1. Metformin	57
10.2. Sulfonylureas	57
10.3. Acarbose.....	57
10.4. Thiazolidinediones.....	58
10.5. Incretin enhancers.....	58
10.6. Incretin mimetics.....	58
10.7. Sodium glucose co-transporter 2 (SGLT-2) inhibitors.....	58
Chapter 11.....	59
Management of cardiovascular risk factors in diabetes	59
11.1 Introduction	59
11. 2. Identifying and assessing cardiovascular disease (CVD) risk	59
11.2.1. Assessment of cardiovascular risk factors	59
11.2.2 Determining CVD Event Risk.....	59
11.3. Screening for presence of cardiovascular disease	62
11.4. Prevention of cardiovascular disease in patients with diabetes and pre-diabetes	63
11.4.1 Lifestyle modification	63
11.4.2 Optimum glycemic control.....	64
11.4.3 Optimum blood Pressure control	64
11.4.4 Antiplatelet therapy.....	65
11.4.5 Lipid-lowering agents	66
Chapter 12.....	68
Complications of diabetes mellitus	68
12.1 Diabetic Retinopathy.....	68
12.1.1. Introduction	68
12.1.2. Background/ Non-Proliferative Diabetic Retinopathy (NPDR)	69

12.1.3. Proliferative Diabetic Retinopathy (PDR).....	69
12.1.4. Diabetic Maculopathy/ Diabetic Macular Oedema (DMO)	70
12.1.5. Care pathway for Diabetic Retinopathy	71
12.1.6. Protocol for screening & referral for Diabetic Retinopathy	72
12.2 Diabetic Neuropathy.....	73
12.2.1 Introduction	73
12.2.2 Diffuse Symmetrical Polyneuropathy (DSPN)	74
12.2.3 Screening and Diagnosis of DSPN.....	75
12.2.4. Management of DSPN	76
12.2.5 Diabetic Autonomic Neuropathies.....	78
12.2.6 Mononeuropathies and atypical neuropathy	81
12.2.7 Diabetic Radiculoplexus Neuropathy	81
12.2.8 Treatment-Induced Neuropathy in Diabetes (Insulin Neuritis).....	81
12.3 Diabetic nephropathy.....	81
Chapter 13.....	82
Diabetic foot	82
13.1. Diabetic foot care service in Sri Lanka.....	82
13.1.1 Community based foot care service for a person with DFD	82
13.1.2 Hospital based foot care service for a patient with DFD	83
13.1.3 Orthotic service for a patient with DFD	84
13.2. Risk stratification and management of a person with DFD.....	84
13.3 Management of a person with a Diabetic foot ulcer.....	86
13.4. Assessment and management of a patient with a diabetes and peripheral arterial disease (PAD).....	88
13.5. Charcot arthropathy	89
Chapter 14.....	91
Management of Diabetic Emergencies.....	91
14.1. The Management of Diabetic Ketoacidosis in Adults.....	91
14.1.1 Diagnostic Criteria.....	91
14.1.2. Pathogenesis	91
14.1.3. Management	92
14.1.4 Resolution of DKA	100
14.1.5. Once resolution of DKA is achieved.....	100
14.2. The management of Hyperosmolar Hyperglycaemic state (HHS)	101
14.2.1. Differences between HHS Vs DKA.....	101
14.2.2. Goals and principles of treatment.....	102
14.2.3. To consider HDU/ICU care	102

14.2.4. Management.....	103
14.2.5. When to discontinue IV insulin and Fluids	106
14.3 Management of Hypoglycaemia in Adults with Diabetes Mellitus	107
14.3.1 Definition	107
14.3.2. Clinical symptoms	107
14.3.3. Management.....	107
Chapter 15.....	110
Management of diabetes in special situations.....	110
15.1 Diabetes in Pregnancy	110
Introduction and Classification of Diabetes in Pregnancy	110
15.1.1 Diabetes in pregnancy: preconception care.....	111
15.1.2 Diabetes in pregnancy: Antenatal Care	113
15.1.3 Intrapartum Care	118
15.1.4 Postnatal Care.....	119
15.1.5 Follow-up Care	119
15.2. Diagnosis and Management of the Metabolic Syndrome	120
15.2.1. Underlying Risk Factors for metabolic syndrome	120
15.2.2. Criteria for Clinical Diagnosis of metabolic syndrome.....	120
15.2.3. Clinical Management of the metabolic syndrome	120
15.2.4. Therapeutic Targets and Recommendations for Clinical Management of metabolic syndrome.....	120
15.3 Management of Diabetes Mellitus (Type 2) in Heart Failure.....	123
15.3.1 Introduction	123
15.3.3 Pathophysiology of heart failure in diabetes mellitus	124
15.3.4 Glycemic Goals in Patients with DM and HF (fig 15.3.2).....	124
15.3.5 Hypoglycaemic agents and its choice in heart failure	125
15.4 Diabetes and Kidney	129
15.4.1 Diabetic Nephropathy	129
15.4.2 Screening and evaluation of DKD	129
15.4.3 Management of DKD	130
15.4.4. Nutrition	136
15.4.5 Lifestyle modifications-	137
15.5 Diabetes and liver	138
15.5.1 Introduction	138
15.5.2 Nonalcoholic fatty liver disease (NAFLD)	138
15.5.3. Prescribing in chronic liver disease	140
15.7 Diabetes management during acute illness in hospital setting	145

15.8. PERI-OPERATIVE CARE IN DIABETES	151
15.8.1 Pathophysiology of Surgical and Anesthetic Stress on Blood Sugar	151
15.8.2 Outcome of Poor Glycemic Control in Peri-Operative Period.....	151
15.8.3 Pre-operative Optimization Prior to Surgery	151
15.8.4. Hospital Admission.....	152
15.8.5 Intra-operative care and management	156
Chapter 16.....	159
Lifestyle modification.....	159
16.1 Exercise in diabetes.....	159
16.1.1 Introduction	159
16.2 Dietary management	162
16.3 Weight management	163
Chapter 17.....	164
Diabetes in different cultural backgrounds	164
17.1 Fasting in Buddhism	164
17.2 Management of diabetes during Ramadan.....	166
17.3 Fasting in Hinduism	169
References.....	170

List of Table

Table 2. 1 Diagnostic criteria for pre-diabetes and diabetes	10
Table 2. 2: Relationship between HbA1c and average plasma glucose level	11
Table 3. 1: Characteristic features of T1DM	14
Table 3. 2: Characteristic features of T2DM	15
Table 3. 3: Characteristic features of slowly evolving immune mediated DM.....	16
Table 3. 4: Characteristic features of ketosis prone T2DM	17
Table 3. 5: Specific subtypes of Diabetes Mellitus	20
Table 3. 6: Drugs or chemicals that can induce diabetes and other genetic syndromes sometimes associated with diabetes	21
Table 5. 1: Monitoring for glycemic control	24
Table 6. 1: Routine evaluations and investigations for people with T2DM at diagnosis and during follow up	28
Table 6. 2: Treatment targets for people with uncomplicated T2DM.....	28
Table 11. 1: Determining CVD events risk	59
Table 11. 2: Determining CVD events risk	67
Table 12. 1: Classification of Diabetic Retinopathy	68
Table 12. 2: Pharmacological agents used in DSPN	77
Table 12. 3: Symptoms and signs associated with Diabetic autonomic Neuropathy	78
Table 13. 1: Risk stratification of developing diabetic foot problems	84
Table 13. 2: Interpretation of Ankle Brachial Pressure Index (ABPI)	88
Table 14. 1: Initial fluid resuscitation, Insulin administration and potassium correction	93
Table 14. 2: Calculation of the insulin dose for weight	95
Table 14. 3: IV Fluid replacement regimen	98
Table 14. 4: Differences between HHS vs DKA.....	101
Table 14. 5: The management of Hyperosmolar Hyperglycaemic state	103
Table15. 1: Pharmacological treatment following delivery	119
Table15. 2: Hemoglobin (HbA1C) goals in patients with Diabetes Mellitus and Heart Failure.....	125
Table15. 3: Albumin quantification	129
Table15. 4: Use of Metformin in patients with CKD	131
Table15. 5:SLGT2i dose adjustments according to level of kidney function	132
Table15. 6: GLP-1RA dose adjustments according to level of kidney function	133
Table15. 7: The use of other hypoglycaemic agents according to level of kidney function	134
Table15. 8:Peri-operative adjustment of anti-diabetic therapies.....	153
Table15. 9 The use of variable rate intravenous insulin infusion (VRIII)	154

List of figures

Figure 1. 1: Pathogenesis of Diabetes Mellitus and mechanism of action of common anti diabetic drugs – the ominous octet.....	04
Figure 1. 2 the Global prevalence of Diabetes Mellitus	06
Figure 1.3 Province specific prevalence D 1	07
Figure 2. 1: Relationship between retinopathy and blood glucose and HBA1C levels	7
Figure 3. 1: Broad classification on different type of diabetes.....	12
Figure 6. 1: Cycle of continuing care for patient centered management of T2DM	26
Figure 6. 2: Determining HbA1C target.....	30
Figure 6. 3: Choice of pharmacotherapy in people with T2DM opting for glycemic control centered strategy	37
Figure 6. 4: Initiation and intensification of Insulin	38
Figure 9. 1: Approximate pharmacokinetic profiles of human insulin and insulin analogues	53
Figure 9. 2: Basal insulin regimen given at night.....	54
Figure 9. 3: Split mixed / pre-mixed insulin regimens	54
Figure 9. 4: Basal bolus insulin regimens	55
Figure 11. 1: WHO/ISH risk prediction Chart.....	60
Figure 12. 1: Non-proliferative Diabetic Retinopathy (NDPR)	69
Figure 12. 2: Proliferative Diabetic Retinopathy	70
Figure 12. 3: PDR with Vitreous Hemorrhage	70
Figure 12. 4: Diabetic Maculopathy	71
Figure 12. 5: Classification of Diabetic Neuropathy	74
Figure 13. 1: Plain X-ray features of early Charcot arthropathy (Five "D"s).....	90
Figure 14. 1 Pathophysiology of Diabetic Mellitus.....	92
Figure 15 1: Classification of diabetes in pregnancy	111
Figure 15. 2 Screenning pathway for diagnosis of pregnancy	115
Figure 15 3: Pathophysiology of heart failure in Diabetes Mellitus.....	124
Figure 15 4 : Individualised HbA1C Targets.....	130
Figure 15 5 : Natural History of NAFLD.....	138
Figure 15 6: Example of basal bolus insulin regimen for the management of non-critically ill patients with T2DM.....	149
Figure 15 7: Management of peri-operative hyperglycemia.....	155
Figure 15 8: Management of perioperative hypoglycaemia	156

List of Annexures

Annexure Number	Content
Appendix 1	PCII protocol floor
Appendix 11	University of Washington [UW] algorithm used for any hyperglycemic ICU patient
Appendix 111	Yale insulin infusion protocol
Appendix 1V	Insulin therapy for parenteral /continuous enteral feeding in the ICU
Appendix V	DDC Protocol
Appendix V1	Insulin administration techniques
Appendix V11	Recommended eating pattern for patients with diabetes

Abbreviations

ACE	Angiotensin Converting Enzyme
ACE inhibitors	Angiotensin-Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
AKI	Acute Kidney Injury
ALA	Alpha-Lipoic Acid
APCS	Asia-Pacific Consensus Statement
ARB	Angiotensin Receptor Blocker
ARRIVE	Aspirin to Reduce the Risks of Initial Vascular Events
ASCEND	A Study of Cardiovascular Events in Diabetes
ASCVD	Atherosclerotic Cardiovascular Disease
ASPREE	Aspirin for Reducing Events in the Elderly
BMI	Body Mass Index
BG	Blood Glucose
BSS	Blood Sugar Series
BW	Body Weight
CAN	Cardiovascular Autonomic Neuropathy
CBG	Capillary Blood Glucose
CCD	Chronic Charcot Disease
CHF	Chronic Heart Failure
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CLI	Critical Limb Ischemia
COTs	Cardiovascular Outcome Trials
CRP	C- Reactive Protein
CSII	Continuous Subcutaneous Insulin Injection
CV risk	Cardiovascular Risk
CV	Central Venous
CPM	Central Pontine Myelinolysis
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CXR	Chest X ray
DAPT	Dual Antiplatelet Therapy
DENO	Diabetic Educator Nursing Officer
DFD	Diabetic Foot Disorder
DFI	Diabetic Foot Infection
DFO	Diabetic Foot Osteomyelitis
DKA	Diabetes Ketoacidosis
DM	Diabetes Mellitus
DMO	Diabetic Macular Oedema
DR	Diabetic Retinopathy
DPP	Dipeptidyl Peptidase-4
DPP-4i	Dipeptidyl Peptidase 4 (DPP-4) Inhibitors
DSPN	Diffuse Symmetrical Polyneuropathy

ECG	Electrocardiogram
ED	Erectile Dysfunction
eGFR	estimated Glomerular Filtration Rate
EWS	Early Warning Score
FBC	Full Blood Count
FBS	Fasting Blood Sugar after 8- 10hours fast
FRII	Fixed Rate Insulin Infusion
GCS	Glasgow Coma Scale
GDM	Gestational Diabetes Mellitus
GLP-1 agonist	Glucagon-like Peptide-1 receptor agonists
GLP-1	Glucagon like Peptide -1
HbA1C	Glycosylated Hb
HDL-C	High Density Cholesterol
HDU	High Dependency Unit
HHS	Hyperosmolar Hyperglycemic State
HIIT	High Intensity Interval Training
HIP	Hyperglycamia in Pregnancy
IAH	Impaired Awareness of Hypoglycaemia
ICR	Insulin to Carb Ratio
ICU	Intensive Care Unit
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IM	Intramuscular
IP/OP	Input and Output
IV	Intravenous
IWGDF	International Working Group on the Diabetic Foot
KCl	Potassium Chloride
LDL-C	Low Density Cholesterol
LMP	Last Menstrual Period
LSCS	Lower Segmental Caesarean Section
MACE	Major Adverse Cardiovascular Event
MALE	Major Adverse Limb Event
MDI	Multiple Daily Injections
MDT	Multi-Disciplinary Team
METS	Metabolic Equivalents
MI	Myocardial Infarction
NG	Naso-Gastric
NICE	National Institute of Clinical Excellence UK
NICE-SUGAR	Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation
Non-CLI	Non-Critical Limb Ischemia
NPDR	Non-Proliferative Diabetic Retinopathy
NS	0.9% Saline (Normal Saline)
OGTT	75 g 2-hour Oral Glucose Tolerance Test
P protocol	Portland protocol

PAD	Peripheral Arterial Disease
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PDR	Proliferative Diabetic Retinopathy
POG	Period of Gestation
PPBS	2-hour Post Prandial Blood Sugar
PPPG	2-hour Post prandial plasma glucose
PTBT	Probe To Bone Test
SGLT2	Sodium-Glucose co-Transporter 2
SMBG	Self-Monitoring of Blood Glucose
SNIRs	Serotonin-Norepinephrine Reuptake Inhibitors
SVS	Society of Vascular Surgeons
SOP	Standard Operating Procedure
SVS	Society of Vascular Surgeons
T1DM	Type 1 Diabetes Mellitus
T2 DM	Type 2 Diabetes Mellitus
TCA	Tricyclic Antidepressants
TDD	Total Daily Dose
TG	Triglycerides
TSH	Thyroid Stimulating Hormone
UW protocol	University of Washington protocol
VBG	Venous Blood Gas
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WHO/ISH	World Health Organization/ International Society of Hypertension
Y protocol	Yale University Protocol

Introduction

The National guideline on diabetes developed defines a set of specific recommendations in the diagnosis and management of patients with Diabetes, its complication and that of diabetes in special situations and will serve as a reference to doctors managing this common condition and its complications.

This guideline was constituted after an extensive literature search and was based on the latest guidelines and consensus agreements from various reputed local, regional, and global organizations.

This document provides necessary practical clinical guidance in secondary and tertiary health care settings in Sri Lanka. Although extensive and comprehensive, this document is not intended to preclude clinical judgment and must be applied in the context of providing excellent clinical care, with adjustments for individual preferences, co-morbidities, and other patient factors.

Methodology and review

Updated information on Diabetes in the literature. The committee relied on systematic methods to evaluate and classify evidence, guided by recently published guidelines from American Diabetes Association (ADA), National Institute of Clinical Excellence (NICE), International Diabetes Federation (IDF), and South Asian Federation of Endocrine Societies (SAFES). An extensive evidence review was done which included literature published in English, and indexed in MEDLINE (through PubMed), the Cochrane Library, Google scholar, Clinical Key and other selected databases. Literature searches focused on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited in this document.

Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence that supports the intervention on the basis of the type, quantity and consistency of data from clinical trials and other sources. The committee has extensively considered the class of recommendations and level of evidence in each statement. However, the recommendations have been modified to suit local context based on local data and resource limitations. When that statement is supported by good quality evidence the term "recommendation" was used and when the evidence is lacking, based on consensus, the term "suggestion" was used

Intended Use

This guideline serves as a resource to the doctors who manage this common condition in the secondary and tertiary care facilities in Sri Lanka. It is comprehensive it and provides practical reference for prevention, detection, evaluation, and management of hyperglycaemia, and hopefully, It will be a cornerstone in improving quality of care in patients with diabetes.

Clinical Implementation

Adherence to recommendations in the guideline can be enhanced by shared decision making between clinicians and patients. However, this document is not intended to preclude clinical judgment and must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, and other patient factors.

Chapter 1

1.1 Introduction and epidemiology

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycaemia. The chronic hyperglycaemia leads to microvascular damage and dysfunction especially the retina, kidneys and nerves and acute metabolic derangements can result in emergencies such as diabetes ketoacidosis and hyperosmolar nonketotic state. In addition, patients with diabetes develop atherosclerosis at an earlier age and more aggressively leading to higher risk of cardio-vascular disease, cerebrovascular disease and peripheral vascular disease. Because of these acute and chronic complications diabetes has become an important cause for mortality and morbidity at a global level.

1.2 Pathogenesis of diabetes

The hyperglycaemia in diabetes is mainly considered to be due to deficiency of insulin hormone or resistance of the target tissues to insulin action or both. The type 1 diabetes is considered to be due to absolute insulin deficiency as a result of beta cell destruction. Type 2 diabetes which is the more common form of diabetes is considered to be due to insulin resistance and inability of the pancreas to overcome the resistance. In addition to type 1 and type 2 diabetes there are several aetiological forms of diabetes which are discussed in detail elsewhere.

In addition to above broader description many other mechanisms have been postulated especially as pathogenetic mechanisms of type 2 diabetes (Fig 1.1) and several other factors have been identified as risk factors for insulin resistance and beta cell dysfunction in type 2 diabetes. Commonly identified risk factors for type 2 diabetes include obesity, sedentary lifestyle, genetics, epigenetics, medications, inflammation, circadian rhythm disruptions and the microbiome.

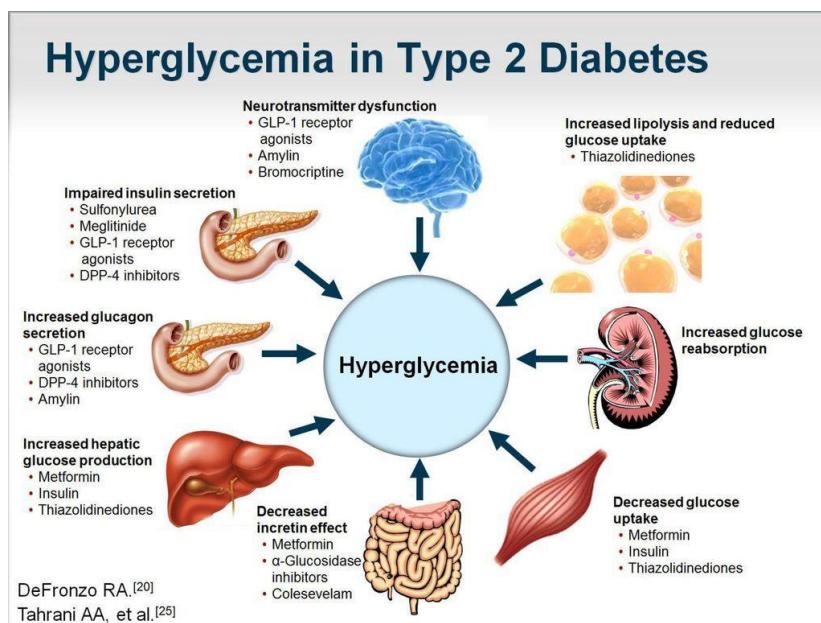


Figure 1. 1: Pathogenesis of Diabetes Mellitus and mechanism of action of common anti diabetic drugs – the ominous octet.

1.3 Diabetes related complications

Diabetes has become a major cause of chronic kidney disease, permanent blindness, myocardial infarction, stroke, and non-traumatic lower limb amputation. Individuals with diabetes have a two- to fourfold increased rate of cardiovascular mortality compared with those without. Incidence of lower extremity amputation has come down in many countries of the world driven mainly by reduction of major lower extremity amputations possibly due to improved care of diabetes and diabetic foot disease. Worldwide, it is estimated that 80% of end stage renal disease (ESRD) cases are due to diabetes or hypertension. Between 2002 and 2015, steep increases (approximately 40–700%) in the incidence of diabetes-associated ESRD were reported in many countries and regions of the world. Retinopathy affects approximately one third of adults with diabetes and represents the leading cause of blindness in these individuals. Population-based studies conducted from the 1990s onwards report a 50–67% lower incidence of diabetic retinopathy compared with earlier studies.

Diabetes, especially the type 2 form is frequently associated with derangements in lipoprotein metabolism as well as other factors such as obesity and hypertension which in combination contribute to significantly increase atherosclerotic cardiovascular risk. Therefore, management of diabetes requires a multi modal, multi-disciplinary approach aimed at reduction of cardiovascular risk and enhanced overall patient wellbeing and not merely blood glucose control.

1.4 History of diabetes

History of diabetes dates back to 1500 B.C. when a disease characterized by the 'too great emptying of urine' was mentioned in Egyptian manuscripts. Indian physicians called it *madhumeha* ('honey urine') because it attracted ants. The ancient Indian physician, Sushruta, and the surgeon Charaka (400–500 A.D.) were able to identify the two types, later to be named Type I and Type II diabetes. First complete description of diabetes was done in the first century A.D. by Aretaeus the Cappadocian, who coined the word *diabetes* (Greek, 'siphon') and dramatically stated "... no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine". Avicenna (980–1037 A.D.), the great Persian physician, in *The Canon of Medicine* not only referred to abnormal appetite and observed diabetic gangrene but also suggested a mixture of seeds (lupin, fenugreek, zedoary) as a treatment. The term *mellitus* (Latin, 'sweet like honey') was coined by the British Surgeon-General, John Rollo in 1798, to distinguish this diabetes from the other diabetes (*insipidus*) in which the urine was tasteless.

1.5 Global epidemiology

According to the World Health Organization (WHO) the number of people with diabetes increased from 108 million in 1980 to 463 million in 2019 (5,6). Global prevalence of diabetes among adults over 18 years of age increased from 4.7% in 1980 to 9.3% in 2019(5, 6). According to IDF diabetes atlas 2019, globally 1 in 11 adults aged 20-79 (463 million people) have diabetes (6). About 50% of them (232 million people) are undiagnosed. 1 in 5 people with diabetes (136 million people) are above 65 years old. 10% of global health expenditure (USD 760 billion) is spent on diabetes. Hyperglycaemia in pregnancy affects 1 in 6 live births (20 million). Over 1.1 million

children and adolescents below 20 years have type 1 diabetes. Overall, 79% of people with diabetes live in low- and middle-income countries like Sri Lanka.

Global prevalence of Diabetes

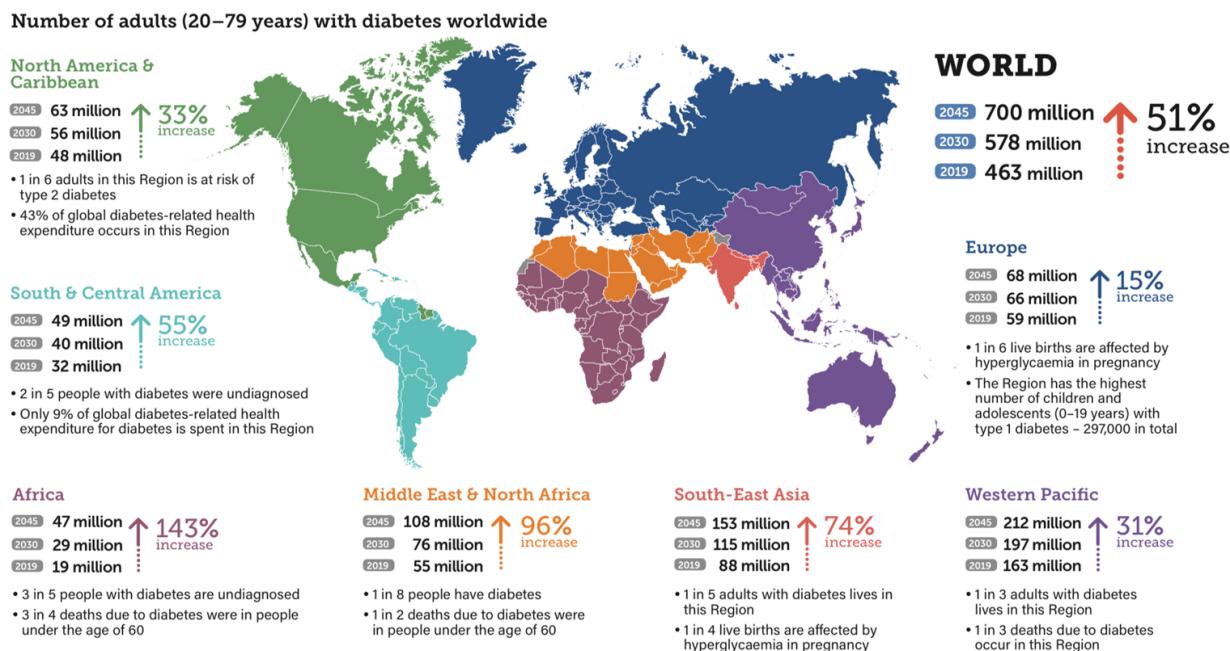


Figure 1. 2 the Global prevalence of Diabetes

Sri Lankan prevalence

In 2008, the prevalence of diabetes among Sri Lankans over the age of 20 years was 10.3% (males 9.8%, females 10.9%) (7). Thirty-six per cent of them were previously undiagnosed. Diabetes prevalence was higher in the urban population compared with rural. The prevalence of pre-diabetes was 11.5%. Those with diabetes and pre-diabetes compared with normal glucose tolerance were older, physically inactive, frequently lived in urban areas and had a family history of diabetes. They had higher body mass index, waist circumference, waist-hip ratio, systolic/diastolic blood pressure, low-density lipoprotein cholesterol and triglycerides. This study also showed disparities of diabetes prevalence in different provinces. The projected diabetes prevalence for the year 2030 was 13.9%. However, Colombo urban study published in 2019 showed an alarming trend with an increase of diabetes prevalence in urban adult population to 27.6% (8). Furthermore, cumulative prevalence of diabetes and prediabetes was 57.9%. While this dramatic change reflects the effect of urbanization and associated change in lifestyle it also reiterates the importance of an up to date evidence based local guideline on management of diabetes. This is also supported by the unpublished data from the Sri Lanka Non-Communicable Disease Survey conducted in 2018 – 2020 period.



Figure1.3 Province specific prevalence D 1

(SLDCS was not conducted in North and the East)

This guideline prepared by the Ceylon College of Physicians aims to provide a comprehensive evidence-based guidance on the management of diabetes and its complications and associated co-morbidities.

Chapter 2

Diagnosis

Introduction

For an individual a diagnosis of diabetes has profound medical and social implications such as potential stigma, life insurance, employment opportunities, driving status, cultural and social opportunities. Therefore, an accurate diagnosis is of paramount importance. Over many years the diagnostic methods as well as cut-offs have evolved. At present only blood glucose and glycosylated haemoglobin are the only tests used in the diagnosis.

The diagnostic cut-offs for diabetes have been derived from epidemiological research in which the association of retinopathy which is a diabetic specific complication has been compared with blood glucose and HbA_{1C} levels (Fig. 2.1).

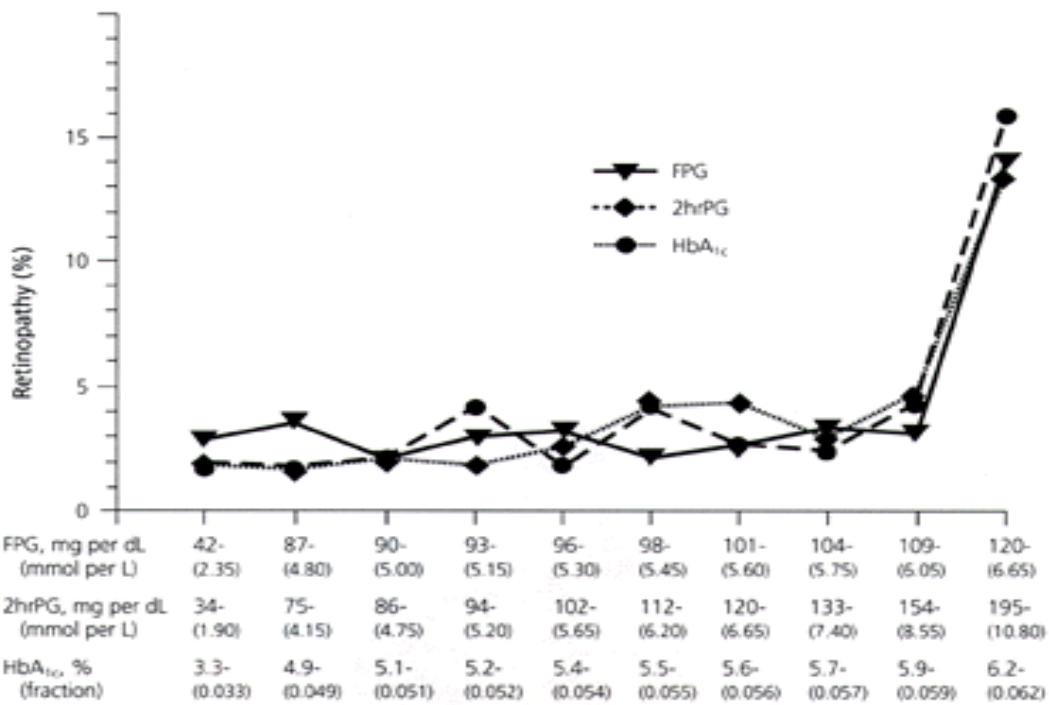


Figure 2. 1: Relationship between retinopathy and blood glucose and HbA_{1C} levels

2.1 Diagnostic tests

Whom to be screened for diabetes?

Screening for diabetes should be undertaken in the following instances:

- Patients presenting with classic symptoms of diabetes (polyuria, thirst and weight loss).
- Patients presenting with infections including tuberculosis
- Patients presenting with microvascular complications

- Patients presenting with cardiovascular or peripheral vascular disease
- Pregnant women Asymptomatic high-risk people

Type 2 diabetes is highly prevalent among Sri Lankans and other South Asians and occurs at a much earlier age (at least a decade earlier) compared to other major ethnic groups. Hence screening of asymptomatic individuals would help identification of those with diabetes and prediabetes at an earlier stage. Early diagnosis would allow early interventions for better outcomes. The criteria for testing for diabetes or prediabetes in asymptomatic adults are shown in the box below.

BOX: 2.1

Testing should be considered in adults with overweight or obesity (BMI 25 kg/m² or 23 kg/m² in Sri Lankans) who have one or more of the following risk factors:

- First-degree relative with diabetes
- History of CVD
- Hypertension (140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >150 mg/dL (1.69 mmol/L)
- Women with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

- ❖ Patients with prediabetes (A1C 5.7% [39 mmol/mol], impaired glucose tolerance, or impaired fasting glucose) should be tested yearly.
- ❖ Women who were diagnosed with GDM should have lifelong testing at least annually.
- ❖ For all other patients, testing should begin at age 35 years*.
- ❖ If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

(Adopted and modified from Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes 2020, American Diabetes Association* consensus expert opinion)

- It is recommended to use fasting plasma glucose (FPG) value, random plasma glucose or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or HbA1C test for diagnosis of diabetes mellitus (Table 3.2)
- FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic screening. However, the concordance between FPG, 2-h PG value during a 75-g OGTT and HbA1c is not always perfect.

2.1.1 FPG, 2-h PG during 75-g OGTT, random plasma glucose

2.1.1.1 Venous plasma glucose should be the standard test.

2.1.1.2 Glucose should be measured immediately after collection. When a blood sample is collected, if immediate analysis is not possible, plasma should be immediately separated, or the sample should be collected into a tube with glycolytic inhibitors and kept in ice until the time of analysis.

2.1.1.3 Fasting is defined as no caloric intake for at least 8 hours.

2.1.1.4 75g OGTT is recommended as a diagnostic test for the following circumstances.

- Impaired fasting glucose (FPG alone fails to diagnose approximately 30% of cases of previously undiagnosed diabetes).
- Gestational diabetes (FPG tends to be lower during pregnancy hence is not appropriate as a single test in the diagnosis of diabetes in pregnancy)
- When HbA1C has discordance with a diagnosis of diabetes
- When a diagnosis of impaired glucose tolerance is needed (OGTT is the only means of identifying people with impaired glucose tolerance (IGT))

2.1.1.5 OGTT should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

2.1.2 HbA1c

2.1.2.1 The HbA1C test should be performed in a laboratory using a method that is (National Glycohemoglobin Standardization Program) NGSP certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay

2.1.2.2 A1C has the following advantages compared with FPG and OGTT

- Greater convenience as no fasting is required
- Greater pre-analytical stability
- Lesser day-to-day variations due to stress, diet, or illness.

Limitations of HbA1c

- Cost
- Availability of the NGSP certified assay
- Interferences in certain conditions

2.1.2.3 Although the concordance between FPG, 2-h PG value during a 75-g OGTT and HbA1c is imperfect, marked discordance should raise the possibility of A1c assay interference due to hemoglobin variants.

2.1.2.4 In conditions that may impact hemoglobin glycation independently of glycemia, such as sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes.

2.1.2.5 Average plasma glucose levels can be approximated using HbA1c levels (Table 2.2)

2.1.3 Random plasma glucose can be used for diagnosis

- o In a patient with classic symptoms of hyperglycaemia (polyuria, thirst, weight loss) and
- o In a patient with hyperglycaemic crisis.

Table 2. 1 Diagnostic criteria for pre-diabetes and diabetes

Diagnostic test	Pre-Diabetes	Diabetes	Comments
Fasting plasma glucose	100* mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)	≥126 mg/dL (7.0 mmol/L)	Fasting is defined as no caloric intake for at least 8 h.
2-h plasma glucose during OGTT	140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)	≥200 mg/dL (11.1 mmol/L)	The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
HbA1c	5.7–6.4% (39–47 mmol/mol)	≥6.5% (48 mmol/mol).	The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay
Random plasma glucose		≥200 mg/dL (11.1 mmol/L)	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

DCCT - Diabetes Control and Complications Trial; **FPG** - fasting plasma glucose; **OGTT** - oral glucose tolerance test; **WHO** - World Health Organization; **2-h PG** - 2-hour plasma glucose

* According to ADA prediabetes criteria 100 to 125mg/dl but WHO defines prediabetes as 110 to 125mg/dl

Table 2. 2: Relationship between HbA1c and average plasma glucose level

HbA1c (%)	Mean Plasma Glucose	
	mg/dl	mmol/l
6	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5
11	310	17.5
12	345	19.5

2.2 Confirming the diagnosis of diabetes

- 2.3.1 In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L), confirms the diagnosis of diabetes.
- 2.3.2 Otherwise diagnosis requires two abnormal test results mentioned above from the same sample or in two separate test samples.
- 2.3.3 If using two separate test samples, the second test, may either be a repeat of the initial test or a different test.
- 2.3.4 If a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated.

2.3 Diagnosis of diabetes in pregnancy

Refer to chapter 15.1

2.4 Aetiological diagnosis of diabetes

Refer to the chapter 3 on Classification of diabetes

Chapter 3

Classification of Diabetes

3.1. Introduction

Hyperglycemia is the universal feature for all types of diabetes. However distinct subtypes which differ in aetiology, underlying pathogenic mechanisms, natural history and response to treatment can be identified.

Classification of diabetes had been evolving from aetiopathological models (e.g., Beta cell-centric models) to novel cluster classification which is based on a constellation of immunological, genetic, epidemiological, metabolic, and clinical variables.

These classifications are meant to optimize diabetes care and precision treatment but are based on additional investigations (C-peptides, beta cell-specific antibodies and genotyping) which are not standardized or not readily available in most clinical settings.

3.2. Types of diabetes

The World Health Organization (WHO) has published classification systems for diabetes since 1965. The most updated WHO classification was published in 2019. Broad categories of diabetes subtypes are presented in **figure 3.1**. The major differences are the inclusion of new categories ("hybrid types of diabetes" and "unclassified diabetes") and removal of subtypes of type 1 diabetes and type 2 diabetes.

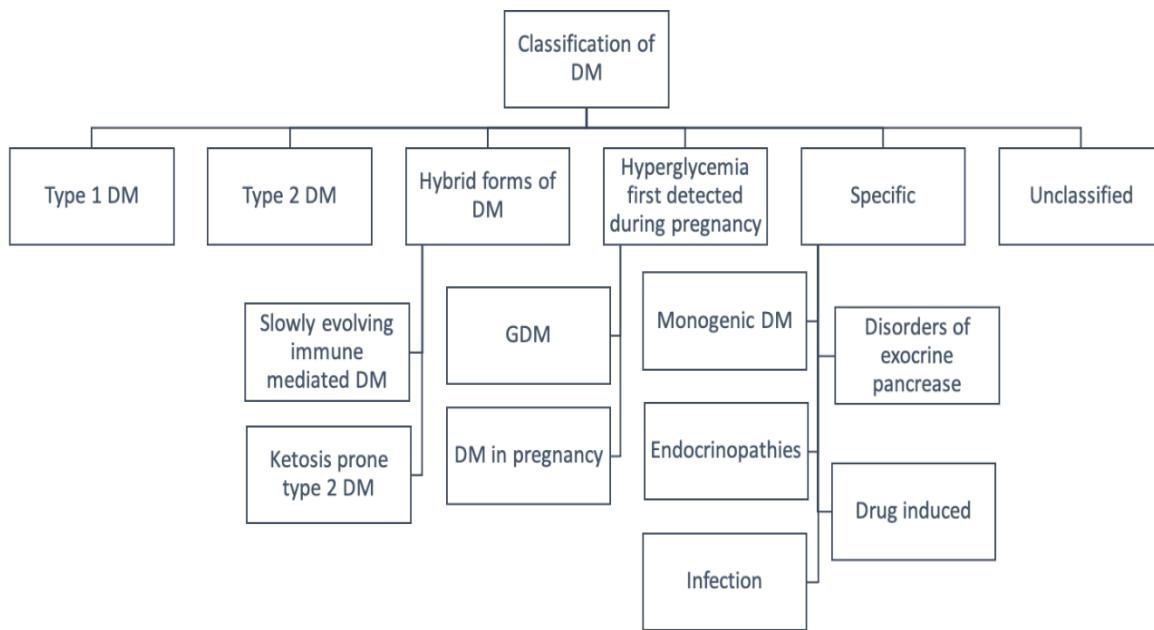


Figure 3. 1: Broad classification on different type of diabetes

(Based on Classification of diabetes mellitus. Geneva: World Health Organization; 2019)

3.3. A practical method of assigning diabetes type in clinical settings

This practical clinical protocol guides clinicians to assign a patient with diabetes at the time of presentation and to decide on treatment options especially insulin therapy when the access to laboratory investigations are limited.

3.3.1 Steps in clinical subtyping when an individual first diagnosed with diabetes

- ✓ Confirm diagnosis of diabetes
- ✓ Exclude secondary causes of diabetes
- ✓ Consider the following which may assist in differentiating subtypes:
 - Age at diagnosis
 - Family history
 - Physical findings, especially presence of obesity and features of syndromic diabetes
 - Presence of features of insulin resistance and metabolic syndrome
 - Presence or absence of ketosis or ketoacidosis
- ✓ Perform diagnostic tests if available (β -cell autoantibodies, C-peptide, genotyping)

A definitive subtyping may not be possible for an individual at the time of diagnosis. Therefore, a rational approach to treatment should be adopted with regular monitoring and review to reduce glucotoxicity and insulin resistance and, to prevent ketosis.

Appropriate assignment to a subtype may be possible over time. For example, the need for longer term insulin vs disappearance of insulin requirement in a patient presenting with ketosis.

3.4. Type 1 Diabetes (T1DM)

Type 1 diabetes was formerly called juvenile diabetes or IDDM (Insulin Dependent Diabetes Mellitus). This type is commoner in the northern hemisphere and predominantly affects children and young adults although no age group is exempted. In Sri Lanka among young adults less than 40 years, type 1 was shown to be 7%.

The cardinal features of patients with T1DM

1. Lower body mass index
2. Use of insulin within 12 months of diagnosis
3. Increased risk of diabetic ketoacidosis
4. Low C peptide
5. Autoantibodies

There is marked variation in the clinical presentation. Characteristic features of T1DM are given in **Table 3.1**.

Table 3. 1: Characteristic features of T1DM

Pathophysiology	Characterized by immune (cellular mediated) or non-immune mediated destruction of the β cells of the pancreas.
Special tests for diagnosis	<p>70-90% of patients have islet autoantibodies at presentation. Rare group of patients will not have autoimmune markers (non-immune type 1 diabetes)</p> <p><i>Islet autoantibodies</i></p> <ul style="list-style-type: none"> • Glutamic acid decarboxylase [GAD-65] antibodies • Islet cell antibodies • Zinc transporter 8 (ZnT8) • Auto-antibodies to insulin • Auto-antibodies to Tyrosine phosphatase IA-2 and IA-2\square <p>Genetics - Strong HLA associations with linkage to DQA and DQB genes in European patients. However, their specific role in pathogenesis is unclear</p>
Clinical Characteristics	<p>Variable presentations are seen</p> <ul style="list-style-type: none"> • Abrupt presentation with DKA (predominantly children and adolescents and rapid beta cell destruction seen) • Modest fasting hyperglycemia rapidly changing to severe hyperglycemia and DKA with infection or other stress. • Rapid remission after initial presentation with DKA or severe hyperglycemia (honeymoon phase) • Decreased insulin requirement for months or years (Predominantly slow destruction seen in adults leading to variable clinical presentation)
Special remarks	<ul style="list-style-type: none"> • Worldwide 5% of all diabetes (7% among young diabetes in Sri Lanka) • Some adults retain sufficient beta cell function to prevent DKA for many years • Often prone to other autoimmune disorders such as Hashimoto's thyroiditis, Grave's disease, Celiac disease, etc.

3.4. Type 2 Diabetes (T2DM)

The worldwide 90-95% of all diabetes is due to T2DM with highest proportions in low- and middle-income countries. T2DM is most common in adults, but an increasing number of children and adolescents are also affected.

Characteristic features of T2DM are shown in Table 3.2.

Table 3. 2: Characteristic features of T2DM

Pathophysiology	<ul style="list-style-type: none">• β-cell dysfunction with relative insulin deficiency• Peripheral insulin resistance• Risk factors for T2DM (Overweight or obesity, increased percentage of body fat distributed predominantly in the abdominal region (sometimes with normal BMI), age, lack of physical activity, gestational diabetes mellitus, hypertension and dyslipidemia, ethnicity (Asian, African American, Hispanic or Latino), family history
Special tests for diagnosis	None
Clinical Characteristics	<ul style="list-style-type: none">• Substantial proportion are asymptomatic and detected incidentally during screening• Some may present with Hyperosmotic symptoms, infections or complications• DKA very rarely occurs spontaneously; when seen, usually arises in association with the stress of another illness such as infection or with the use of certain drugs (e.g., corticosteroids, atypical antipsychotics, and sodium-glucose cotransporter 2 inhibitors)
Special remarks	<ul style="list-style-type: none">• 90-95% of all diabetes (90% in young Sri Lankan adults)• Incidence is increasing among children and adolescents due to increasing childhood obesity

3.5. Hybrid forms of DM

Some adults will have clinical features of both T1DM & T2DM at the diagnosis, creating a diagnostic dilemma. Slowly evolving immune-mediated diabetes and ketosis prone T2DM are newly proposed nomenclature for these types of patients.

3.5.1. Slowly evolving immune-mediated diabetes

A group of patients with slowly evolving forms of diabetes which clinically present like T2DM but have evidence of pancreatic autoantibodies has been recognized. This form of diabetes was referred to as "latent autoimmune diabetes in adults" (LADA). A similar subtype has been described in children and adolescents and was referred to as latent autoimmune diabetes in youth (LADY).

Characteristic features of slowly evolving immune mediated DM are given in **table 3.3.**

Table 3. 3: Characteristic features of slowly evolving immune mediated DM

Pathophysiology	<ul style="list-style-type: none"> Slowly evolving immune-mediated destruction of pancreatic β-cells
Special tests for diagnosis	<ul style="list-style-type: none"> Glutamic acid decarboxylase (GAD) Protein tyrosine phosphatase IA-2 Anti-insulin antibodies ZnT8
Clinical characteristics	<ul style="list-style-type: none"> Positivity for GAD autoantibodies Age older than 35 years at diagnosis Not needing for insulin therapy in the first 6–12 months after diagnosis
Special remarks	<p>Differentiating features from type 1 DM</p> <ul style="list-style-type: none"> Obesity Features of the metabolic syndrome Retaining greater β-cell function Expressing a single autoantibody (particularly GAD65) Carrying the transcription factor 7-like 2 (TCF7L2) gene polymorphism

3.5.2. Ketosis prone T2DM

This unusual and rare form of non-immune ketosis-prone diabetes was first reported in young African Americans in Flatbush, New York, USA and hence was termed Flatbush diabetes. Similar phenotypes were described in populations in sub-Saharan African.

Characteristic features of ketosis prone T2DM are given in **table 3.4**.

Table 3. 4: Characteristic features of ketosis prone T2DM

Pathophysiology	<ul style="list-style-type: none">Transient secretory defect of β-cells with remarkable recovery of insulin-secretory capacity during the period(s) of remissionGlucose toxicity may contribute to the acute and phasic β-cell failureNo genetic or autoimmune etiology recognized
Special tests for diagnosis	<ul style="list-style-type: none">None
Clinical characteristics	<ul style="list-style-type: none">Typically present with ketosis and severe insulin deficiency but later go into remission not requiring insulin treatment.Subsequent clinical course more closely resembled T2DM90% of patients can get recurrent ketosis within 10 years
Special remarks	<ul style="list-style-type: none">First reported in young African Americans in Flatbush, New York, USA and subsequently in AfricansRare in Europeans and South Asians

3.6. Hyperglycemia first detected in pregnancy

The new classification includes two categories of hyperglycemia when first recognized in pregnancy.

1. Diabetes mellitus; defined by the same criteria as in non-pregnant persons
2. Gestational diabetes: defined by newly recommended glucose cut-off points that are lower than those for diabetes (Detected during screening between 24 and 28 weeks of gestation)

3.7. Other specific types of diabetes

Several specific subtypes that do not fall into above categories have been categorized (**Table 3.5**).

3.7.1. Monogenic diabetes

There have been considerable advances in molecular genetics of diabetes over the last two decades. These advances have led to identify clinical subgroups and have resulted in the recognition of new genetic syndromes. Most importantly it has been shown that genetic diagnosis can result in improved treatment outcomes for some people, even in a small proportion of those with diabetes. Two broad categories of monogenic diabetes i.e., monogenic defects of β-cell function and monogenic defects of insulin action have been identified.

3.7.1.1. Monogenic defects of β -cell function

- Clinical subtypes due to monogenic defects in β -cell function include maturity-onset diabetes of the young (MODY), permanent neonatal diabetes (PNDM), transient neonatal diabetes (TNDM), and genetic syndromes where insulin-deficient diabetes is associated with specific clinical features.
- A subtype of autosomal dominantly inherited early-onset familial diabetes (generally with onset before the age of 25 years) that does not require insulin initially was recognized clinically as MODY. The basic pathophysiology was β -cell dysfunction. Mutations in the glucokinase gene (GCK MODY) and hepatocyte-nuclear factor gene (HNF1A MODY and HNF4A MODY) are the commonest. In GCK MODY life-long mild fasting hyperglycemia is seen and patients rarely develop microvascular complications and hence do not require pharmacological treatment. HNF1A MODY is the commonest form and results in progressive and marked hyperglycemia with a high risk of microvascular and macrovascular complications. However, these patients are sensitive to the hypoglycaemic effects of sulfonylureas.
- Monogenic diabetes that occurs before six months of age is termed monogenic neonatal diabetes. About 50% have transient form (TNDM) that resolves spontaneously majority (~70%) having abnormalities in the chromosome 6q24 region. Those who have permanent neonatal (PNDM) have mutations in KCNJ11 or ABCC8 genes which encode the Kir6.2 and SUR1 subunits of the ATP-sensitive potassium channel (KATP channel). Hence these individuals can be treated with oral sulfonylureas without insulin like in HNF MODY.
- Heteroplasmic mitochondrial gene mutation at position 3243 leads to maternally inherited diabetes and deafness (MIDD) with sensor-neural deafness and diabetes. Some of them also have myopathy, pigmented retinopathy, cardiomyopathy, and focal glomerulosclerosis. Several multisystem monogenic syndromes with marked β -cell dysfunction have been described. Wolfram's syndrome (WFS1 and WFS2) due to autosomal recessive inheritance characterized by severe insulin-deficiency is associated with optic atrophy, diabetes insipidus, and neural deafness (DIDMOAD).

3.7.1.2. Monogenic defects of insulin action

- Less common than monogenic β -cell defects. Characterized by features of insulin resistance (hyperinsulinemia, acanthosis nigricans, polycystic ovarian disease and virilization) without having obesity. Mutations in the insulin receptor gene leads to several hyperglycemic syndromes. Extreme insulin resistance, dysmorphism, severe intra-uterine retardation and early mortality is seen in two pediatric syndromes, Leprechaunism and Rabson-Mendenhall syndrome.
- Insulin resistance and lipodystrophy are seen in familial partial lipodystrophy due to mutations in the LMNA gene coding for nuclear lamin A/C and early onset diabetes due to PPARG mutations.

3.7.2. Diseases of the exocrine pancreas

- Processes such as pancreatitis, trauma, infection, pancreatic cancer and pancreatectomy that diffusely damages the pancreas can cause diabetes. Cystic fibrosis leads to both exocrine pancreatic failure and reduced insulin secretion.
- However, the exact relationship between these two defects is not clear. Abdominal pain and pancreatic calcification on X-ray or ultrasound and ductal dilatation are characteristic features in Fibrocalculous pancreatopathy.

3.7.3. Endocrine disorders

- Excess secretion of hormones that have anti insulin actions (e.g., growth hormone, cortisol, glucagon, epinephrine) leads diabetes (e.g., acromegaly, Cushing's syndrome, glucagonoma and phaeochromocytoma).
- Successful treatment of the condition causing hormone excess usually leads to resolution of diabetes. A rare endocrine tumour somatostatinoma inhibits insulin secretion and causes hyperglycemia.

3.7.4. Drug or chemical-induced diabetes

Drugs that can affect insulin secretion or insulin action (**Table 3.6**) can precipitate diabetes in persons with insulin resistance or moderate β -cell dysfunction.

Table 3. 5: Specific subtypes of Diabetes Mellitus

Monogenic diabetes Monogenic defects of β-cell function (mutated gene followed by clinical syndrome)	Monogenic defects in insulin action (mutated gene followed by clinical syndrome)
GCK MODY HNF1A MODY HNF4A MODY HNF1B RCAD mtDNA 3243 MIDD KCNJ11 PNDM KCNJ11 DEND 6q24 TNDM ABCC8 MODY INS PNDM WFS1 Wolfram syndrome FOXP3 IPEX syndrome EIF2AK3 Wolcott-Rallison syndrome	INSR Type A insulin resistance INSR Leprechaunism INSR Rabson-Mendenhall syndrome LMNA FPLD PPARG FPLD AGPAT2 CGL BSCL2 CGL
Abbreviations: MODY = maturity-onset diabetes of the young; RCAD = renal cysts and diabetes; MIDD = maternally inherited diabetes and deafness; PNDM = permanent neonatal diabetes; TNDM = transient neonatal diabetes; DEND = developmental delay epilepsy and neonatal diabetes.	Other generic syndromes sometimes associated with diabetes Table 3.6 Abbreviations: FPLD = familial partial lipodystrophy; CGL = congenital generalized lipodystrophy
Diseases of the exocrine pancreas Fibrocalculous pancreatopathy Pancreatitis Trauma/pancreatectomy Neoplasia Cystic fibrosis Haemochromatosis Others	Endocrine disorders Cushing's syndrome Acromegaly Phaeochromocytoma Glucagonoma Hyperthyroidism Somatostatinoma Others
Drug- or chemical-induced diabetes Table 3.6	Uncommon forms of immune-mediated diabetes
Infections Congenital rubella Cytomegalovirus Others	Insulin autoimmune syndrome (autoantibodies to insulin) Anti-insulin receptor antibodies «Stiff man» syndrome Others
Other clinically defined subgroups	Diabetes associated with massive hypertriglyceridaemia

*This is a list of the most common types in each category but is not exhaustive

3.7.5. Infection-related diabetes

Coxsackie B, cytomegalovirus, adenovirus and mumps and several other viruses have been implicated in inducing T1DM but their role in its aetiology is uncertain. Diabetes has been recognized in some people with congenital rubella.

Table 3. 6: Drugs or chemicals that can induce diabetes and other genetic syndromes sometimes associated with diabetes

Drugs or chemicals that can induce diabetes	Other genetic syndromes sometimes associated with diabetes
<ul style="list-style-type: none">▪ Glucocorticoids▪ Thiazides▪ Alpha-adrenergic agonists▪ Beta-adrenergic agonists▪ Phenytoin▪ Pentamidine▪ Nicotinic acid▪ Pyrinuron▪ Thyroid hormone▪ Interferon-alpha Others	<ul style="list-style-type: none">▪ Down syndrome▪ Friedreich's ataxia▪ Huntington's chorea▪ Klinefelter's syndrome▪ Lawrence-Moon-Biedel syndrome▪ Myotonic dystrophy▪ Porphyria▪ Prader-Willi syndrome▪ Turner's syndrome Others

3.7.6. Uncommon specific forms of immune-mediated diabetes

- Diabetes has been described in several immunological diseases with a different pathogenesis to T1DM. Hyperglycemia sufficient to be called diabetes but more commonly hypoglycaemia has been reported in individuals who develop insulin autoantibodies.
- Antibodies that bind to insulin receptors can also cause diabetes by reducing the binding of insulin to target tissues as well as hypoglycaemia due to insulin agonist effect on the receptor. People with insulin receptor autoantibodies often have acanthosis nigricans and this syndrome was termed Type B insulin resistance in the past.
- In the "stiff man syndrome" where about 50% develop diabetes is an autoimmune disorder of the central nervous system, characterized by stiffness of the axial muscles with painful spasms is associated with very high titers of GAD65 autoantibodies.

3.7.7. Other genetic syndromes sometimes associated with diabetes

Several genetic syndromes associated with an increased incidence of diabetes have been described (See **table 3.6** for details).

3.8. Unclassified Diabetes

With increasing availability of autoantibodies, molecular genetic diagnostics subtyping diabetes has become increasingly complex. Hence a subtype has been proposed to classify patients who cannot be assigned to a distinct form until the proper diagnosis is made.

Chapter 4

Prediabetes

4.1. Introduction

- 'Prediabetes' is the term used to describe individuals who have glucose range above normal but who do not meet the criteria to diagnose diabetes.
- Prediabetes is defined as any one of the following: impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and raised HbA1C.

4.2. Diagnosis

The following are the criteria to define Prediabetes. The presence of any one of the three is considered as Prediabetes.

- Fasting plasma Glucose 100-125mg/dl (5.6-6.9mmol/L) – IFG
- 2-hour PPG after 75-g glucose 140-199mg/dl (7.8-11mmol/L)- IGT
- HbA1C 5.7-6.4% (39-47mmol/L)

4.3. Cardiovascular risk

- Prediabetes is not a disease entity in itself. It is important to identify individuals with prediabetes as they have a higher risk of developing diabetes and cardiovascular disease (CVD). Prediabetes is associated with risk factors for CVD and diabetes: Obesity (commonly visceral and abdominal obesity), insulin resistance, high triglycerides, low HDL cholesterol and hypertension.
- In a meta-analysis of 16 studies that had followed up 44,203 participants, it was demonstrated that the incidence of diabetes in future was increased with HbA1C above 5%: 5-year incidence of diabetes was 9-25% if the HbA1C was 5.5-6%, and 25-50% if the HbA1C was 6-6.5%.

4.4. Management of Prediabetes

- Patients should be counselled about their higher risk of diabetes and CVD.
- It is appropriate to risk screen these individuals for CVD, non-alcoholic fatty liver disease and hypertension.
- Lifestyle modification has been shown in many studies to be an effective tool for prevention of diabetes. Intensive lifestyle modification that includes a lower calorie diet and exercise regime has been shown to reduce the risk of diabetes risk, all-cause mortality, and cardiovascular mortality and microvascular complications in those with prediabetes.
- Appropriate goals for prevention of diabetes in individuals with Prediabetes are as follows
 - Weight loss goal of 7-10%
 - Exercise regime of 150minutes per week
 - A lower calorie plan that is 500 to 1000 calories less than the individual requirement
- Metformin therapy may be used for prevention of diabetes in those with obesity or those with previous gestational diabetes mellitus

Chapter 5

Clinical and laboratory evaluation of disease progression, complications and assessment of glycemic control

5.1. General Recommendations

5.1.1. Complete medical evaluation should be performed at the initial visit to confirm and classify diabetes, evaluate diabetes related complications and potential co-morbid conditions.

5.1.2. Follow up visits should include

- Medical history and physical evaluation
- Laboratory evaluation for attainment of glycaemic and metabolic targets
- Assessment of risk for complications
- Assessment of medication taking behaviors, intolerance, and side-effects
- Diabetes self-management behaviors, nutrition, and psychosocial health

5.1.3. Interval follow-up visits should occur at least every 3-6 month, individualized to the patient. Annual screening for diabetes related end-organ damage should be arranged at least annually

5.2. Recommendations for HbA1c Testing

5.2.1. Perform **the HbA1c test at least twice a year** in patients who are meeting treatment goals (and who have stable glycemic control).

5.2.2. Perform the HbA1c test quarterly in patients whose therapy has changed between the two HbA1c tests or who are not meeting glycemic goals.

5.2.3. An HbA1c goal for many nonpregnant adults of **<7%** (53 mmol/mol) is appropriate.

5.2.4. On the basis of provider judgement and patient preference, achievement of lower HbA1c levels (such as **<6.5%**) may be acceptable if this can be achieved safely without significant hypoglycaemia or other adverse effects of treatment.

5.2.5. Less stringent A1C goals (such as **<8%** [64 mmol/mol]) may be appropriate for patients with:

- A history of severe hypoglycaemia
- Limited life expectancy
- Advanced microvascular or macrovascular complications
- Extensive comorbid conditions
- Long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.

5.2.6. Investigate unexplained discrepancies between HbA1c and other glucose measurements. Seek advice from a team with specialist expertise in diabetes or clinical biochemistry

5.2.7. If HbA1c monitoring is invalid because of disturbed erythrocyte turnover or abnormal haemoglobin type, estimate trends in blood glucose control using one of the following:

- Quality-controlled plasma glucose profiles
- Fructosamine estimation

5.3. Monitoring for glycemic control/ development of complications

Table 5. 1: Monitoring for glycemic control

Tests/ Procedures	Frequency	Target
HbA1c	At least 2 times/year if stable Quarterly if treatment changes or not meeting goals	HbA1c <7% (May vary depending on individualized targets)
Blood pressure	Measure at every routine clinic visit	<BP: 140/90 BP:<130/80 in high-risk patients
Lipid profile	Initial visit and annually, or more frequently if lipids are high and after treatment has been initiated	TC <200 LDL<100; High risk <70 TG < 150
Weight/BMI/Waist	Weigh and measure waist at each regular diabetes visit BMI annually	BMI 18-23 kg/m ² Waist: < 80cm in females < 90 cm in males
Microalbumin	Initial visit and annually if no persistent dipstick proteinuria. Twice annually if urinary albumin >30 mg/g creatinine and/or an eGFR <60 mL/min/1.73 m ²	<30 mg/g Creatinine
Serum Creatinine	Initial visit and annually	
Liver enzymes	Initial visit and annually to identify presence of fatty liver	
Eye examination for retinopathy	Annual or more frequent if significant retinopathy present	
Comprehensive foot examination	Initial visit and annually if evidence of sensory loss/prior ulceration/amputation – feet should be inspected at every visit	
Peripheral neuropathy	Annually, with a careful history and assessment of small fibre (temperature or pinprick sensation) and large fibre function (vibration sensation using 128Hz tuning fork). Annually, 10-g monofilament testing to identify feet at risk for ulceration and amputation	

5.4. Cardiovascular Disease

Recommendations for screening

5.4.1. Assess for established cardiovascular disease (CVD) at the initial visit

- Coronary artery disease: symptoms of coronary artery disease or abnormal ECG or both
- Assess for features of other cardiovascular disease including stroke and peripheral vascular disease.

If established CVD, appropriate steps to be secondary prevention including lifestyle modification/ Statin/ Antiplatelet.

5.4.2. CVD risk factor assessment (looking for the presence of hypertension, dyslipidaemia, cigarette smoking, obesity, physical inactivity, albuminuria, family history of premature cardiovascular disease) to be carried out at the initial visit and annually thereafter.

5.5. Erectile Dysfunction

Recommendations for screening

5.5.1. Offer men with T2DM the opportunity to discuss erectile dysfunction as part of their annual review

5.5.2. Assess, educate, and support men with T2DM who have problematic erectile dysfunction, addressing contributory factors such as cardiovascular disease as well as possible treatment options.

5.6. Chronic Kidney Disease

Recommendations for screening refer to chapter 15.4

5.7. Diabetic Retinopathy

Recommendations for screening refer to chapter 12.1.6

5.8. Neuropathy

Recommendations for screening refer to chapter 13.2

5.9. Foot screening

Recommendations for screening refer to chapter 13

Chapter 6

Management of type 2 diabetes

6.1 Introduction

Management of people living with diabetes requires a patient centered multi-disciplinary approach. This section provides guidance on overall management considerations with special emphasis on pharmacotherapy. Individual circumstances, patient characteristics and concerns and availability of resources should be taken into consideration with each patient and clinical judgment should be exercised in making management decisions.

Management goals and plan

Broad management goals for a patient with T2DM are to

- Prevent morbidity
- Improve quality of life and
- Improve survival

This requires a patient-centered multi-disciplinary approach and a cycle of continuing care (figure 6.1).

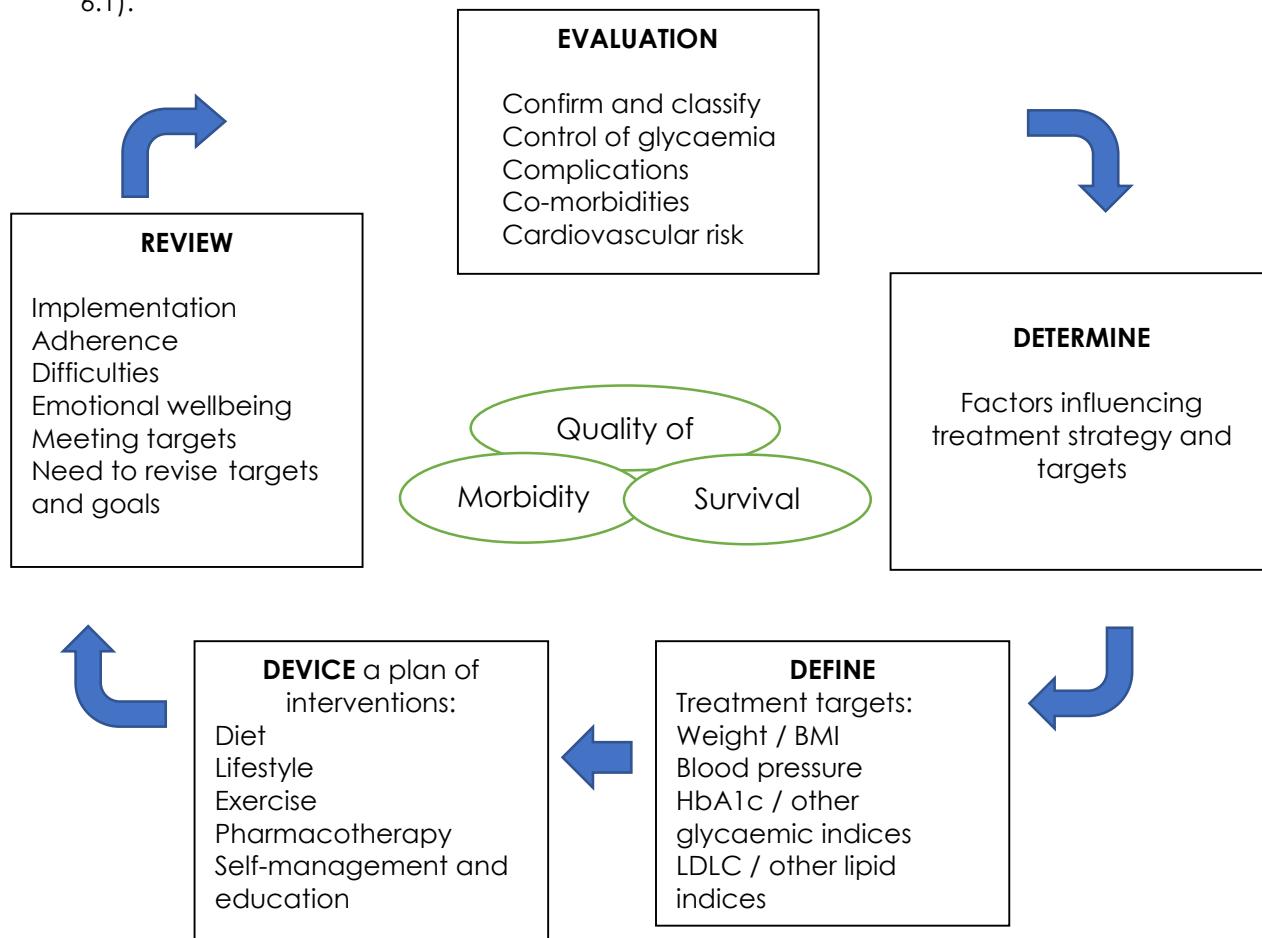


Figure 6. 1: Cycle of continuing care for patient centered management of T2DM

(Adopted from American Diabetes Association Standards of Medical Care in Diabetes-2020)

6.1.1 EVALUATION

6.1.1.1. It is recommended that all patients with newly diagnosed T2DM should be comprehensively evaluated for complications and co-morbidities at the time of diagnosis.

The recommended plan for evaluation of a patient with newly diagnosed T2DM is outlined in Box 6.1.

Box 6.1. Evaluation of a patient with T2DM on diagnosis

CLINICAL EVALUATION

Risk factors for ASCVD

Family history of premature ASCVD
Weight and body mass index

Smoking / alcohol / substance use
Blood pressure

Established ASCVD

Angina, stroke, TIA, intermittent claudication, rest pain, ischaemic ulcers/ gangrene

Diabetic foot assessment

- Neuropathy (10g monofilament test, vibration sensation with 128 Hz tuning forks or vibration perception threshold with biothesiometer)
- Ischaemia – dorsalis pedis and posterior tibial pulses, ankle brachial pressure index
- Deformity- Pre-ulcer lesions – callosity, corn, in-grown toenail, toe web fungal infection
- Ulcer-gangrene, amputations

Diabetic retinopathy screening

- Visual acuity
- Dilated fundoscopy

INVESTIGATIONS

Glycaemic control

HbA1c Fasting plasma glucose Post prandial plasma glucose

Nephropathy screening

Urinalysis Spot urine albumin:creatinine or protein:creatinine ratio

Serum creatinine, eGFR and electrolytes

Co-morbidities

Lipid profile Liver enzymes ECG

- Additional evaluation and / or referral is recommended if abnormalities are found in any of the above investigations

Patients with diabetes require lifelong follow up with periodic monitoring. Frequency for monitoring above parameters are outlined in **table 6.1**.

Table 6. 1: Routine evaluations and investigations for people with T2DM at diagnosis and during follow up

Evaluation / investigation	During treatment titration / until treatment goal is achieved	If normal or once stable on target
HbA1c	3 monthly	6-12 monthly
Lipid profile	3 monthly	12 monthly
AST, ALT	1-3 monthly or more frequently depending on severity and trend	12 monthly
Serum creatinine and electrolytes	1-3 monthly or more frequently depending on the severity and trend	12 monthly
UACR / UPCR	3-6 monthly	12 monthly
Diabetes retinopathy screening	According to clinical assessment	12 monthly
Foot assessment	According to clinical assessment	12 monthly

6.1.2 TREATMENT TARGETS AND DETERMINANTS

Individualized treatment targets should be discussed with the patient and agreed upon. Benefits of achieving the targets should be weighed against the risks of attempting to reach those targets, with the final goals being improving quality of life, morbidity and survival.

For a patient with T2DM, without other comorbidities and complications, and having low risk of hypoglycaemia, the preferred targets are summarized in table 6.2.

Table 6. 2: Treatment targets for people with uncomplicated T2DM

Parameter	Target
HbA1c	< 7%
Fasting plasma glucose	70-130 mg/dL
Post prandial plasma glucose*	< 180 mg/dL
LDL cholesterol	100 mg/dL
Blood pressure**	130/80 mmHg
Body weight	5-10% weight loss for people who are overweight / obese

* Those with lower risk of hypoglycaemia PPG <140mg/dl may be considered.

** Commence treatment when BP >140/90mmHg. In those above 65 years blood pressure target needs to be 140/80)

Glycaemic target: stringent Vs less stringent

Lowering blood glucose decreases the risk of microvascular and macrovascular complications. However, overly stringent glucose lowering invariably increases the risk of hypoglycaemia and may increase mortality, particularly in the vulnerable populations.

6.1.2.1. It is recommended that for people at high risk of hypoglycaemia and/or its consequences, a less stringent HbA1c target (7.5 - 8.0%) should be adopted.

These patient groups include:

- Elderly
- Having multiple comorbidities and / or ASCVD
- Short life expectancy
- Previous hypoglycaemic events
- Hypoglycaemic unawareness
- High risk occupations – driving, machine operators, working in heights
- Limited healthcare access

Older patients with comorbidities are at increased risk of hypoglycaemia. Aiming a stringent glycaemic control may increase the risk of hypoglycaemia, cardiovascular events and mortality.

6.1.2.2. It is recommended that for young patients, with long life expectancy, without other comorbidities or previous significant hypoglycaemic events, and intact hypoglycaemia awareness and low risk occupations with readily access to healthcare services should be offered more stringent HbA1c target (<6.5%)

- Lowering HbA1c reduces microvascular and macrovascular complications of diabetes.
- Achieving stringent control in the early phases of the disease will have long lasting beneficial effects irrespective of the glycaemic status in later stages (ie legacy effect).
- Therefore, intensive glucose control should be offered for patients at lower risk of hypoglycaemia. Discuss the benefits and risks of tight glycaemic control with the patient and consider the patient's preference in setting individualized goals (see **figure 6.2**).

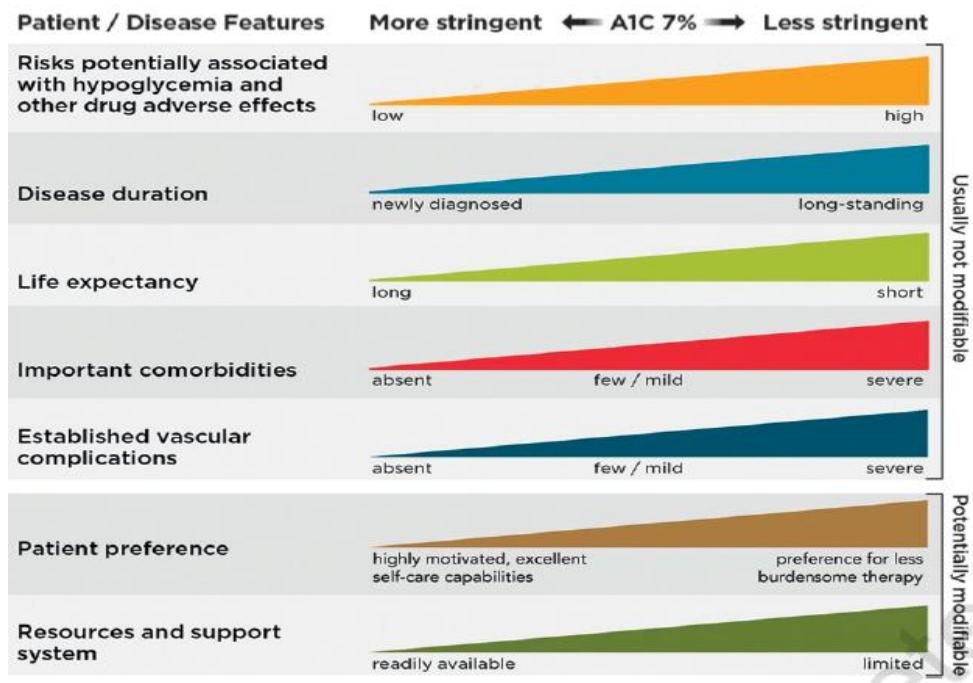


Figure6. 2: Determining HbA1C target

(Adopted from American Diabetes Association Standards of Medical Care in Diabetes 2020)

Lipid targets Consider future atherosclerotic cardiovascular disease risk in determining the lipid targets.

Discuss with the patient regarding the benefits of treatment and safety of lipid lowering therapies in setting individualized goals. See chapter 11 on lipid management in diabetes.

Blood pressure targets

Consider age, risk of hypotension (autonomic neuropathy, risk of falls), renal and cardiac functions, and complexity of treatment and patient preferences in determining blood pressure target. See chapter 11 on blood pressure management in this book and The National Guideline on Management of hypertension for secondary and tertiary care for further reference.

Weight targets

Weight loss is effective in improving glycaemic control, metabolic indices and preventing complications of diabetes. Target weight should be determined by considering pre-intervention weight and body mass index, presence of comorbidities (fatty liver, obstructive sleep apnoea), dietary habits and preferences, exercise capacity (cardiopulmonary reserve, articular diseases) and patients preference. See section 16.3 on weight management for further details.

6.1.3. PLAN OF MANAGEMENT

Diabetes management requires a multi-modal strategy. Dietary control, active lifestyle, regular physical exercise, pharmacotherapy are integral components.

6.1.3.1. It is recommended that all patients with diabetes should be educated and trained in diabetes self-management)

Education and training on diabetes self-management improves glycaemic control, quality of life (6), all-cause mortality and healthcare cost. This is best achieved through a structured education programme, delivered through trained health care providers (medical officers, Diabetes Education Nursing Officers [DENO] etc.), at diagnosis, periodic reviews, detection of complications and at transitions of care. Need for shared decision making and respect for patient preferences and wishes are emphasized.

6.1.4. REVIEW

Regular reviews are necessary to ascertain success of implementing the interventions and to identify difficulties and provide solutions. Provision of emotional support and motivation should be an integral component. All patients should be inquired about barriers to follow lifestyle and pharmacological treatment strategies, including adverse effects, difficulties accessing treatment and perceptions. All patients should be inquired about hypoglycaemia (frequency, severity, awareness, timing and causes). Periodic evaluation for disease control and complications should continue as outlined in section 6.1.1.

6.2. Pharmacological interventions for diabetes management

6.2.1. It is recommended that all patients diagnosed to have T2DM, should be commenced on lifestyle management to improve glycaemic control.

Lifestyle modification focusing on diet, physical activity and exercise, improves glycaemic control, body weight and blood pressure favorably thereby decreasing the risk of cardiovascular disease and other complications of diabetes.

6.2.2 It is recommended that all patients diagnosed to have T2DM, should be commenced on metformin unless contraindicated.

6.2.3 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated. Other agents, including insulin, may be added to metformin

- Metformin is the preferred first line therapy considering its beneficial effects on glucose control, weight control and less hypoglycaemia compared to other agents, in particular to sulfonylureas. Its glucose lowering efficacy was comparable to other agents except DPP4i which had a lower efficacy. This is of low cost and has a good safety profile with experience over several decades without major adverse effects on long term use.
- A specific advantage of using metformin is that it can be combined with any other glucose lowering therapy including insulin.

6.2.4 If metformin is not tolerated or is contraindicated, an alternative agent should be selected. Follow the principles in recommendations in selecting the alternative glucose lowering medication.

Although some glucose lowering agents in SGLT2i and GLP1RAs drug classes have shown cardiovascular and renal benefits, particularly in patients at high risk for cardiovascular and renal disease, their role as initial monotherapy is still unclear.

6.2.5 Adding a second glucose lowering agent should be considered in the following circumstances:

- Glycaemic control above target despite good adherence to lifestyle and medical therapy
- Compelling indication due cardiovascular or renal disease
Achieving individualized glycaemic control targets decrease microvascular and macrovascular complications and improves survival. As T2DM leads to progressive beta cell failure, treatment needs to be escalated over the years adding more agents, to maintain glycaemia within target. Even in individuals who have achieved desired glycaemic target, addition of another agent for cardiovascular and or renal benefit and appropriate titration may be considered.

6.2.7 When HbA1c is above 10% and / or patient has features of insulinopaenia it is reasonable to use insulin with or without another oral agent as the initial therapy

6.2.8 When HbA1c is between 8 to 10%, it is reasonable to start with combination therapy. Initiation of combination therapy allows faster attainment of glycaemic control and may delay the onset of primary and secondary oral glucose-lowering therapy failure

6.2.9 In a setting where cost of treatment is not a limitation, for a patient with T2DM and;

6.2.9.1 Established ASCVD, it is recommended to add a SGLT2i or GLP1RA with proven cardiovascular benefit. SGLT2 inhibitors improve cardiovascular outcomes in patients with diabetes and established ASCVD. Empagliflozin and canagliflozin reduce all-cause mortality. GLP1RAs improve cardiovascular events and mortality. Benefit is seen in people with established cardiovascular disease and these may be beneficial in the setting of primary prevention.

6.2.9.2 Having or at risk of developing heart failure, it is recommended to add an SGLT2i proven to reduce hospitalizations due to heart failure. SGLT2 inhibitors reduce hospitalizations due to heart failure. Empagliflozin, canagliflozin and dapagliflozin improve cardiovascular outcomes mainly by reducing heart failure hospitalizations.

6.2.9.3 Chronic kidney disease, it is recommended to add a SGLT2i. Empagliflozin, canagliflozin and dapagliflozin improve renal outcomes related to proteinuria and progression of renal impairment. Glucose lowering efficacy is minimal when GFR is less than 45 mL/min/1.73m². However, cardiovascular and renal benefits are proven for GFR above 30 mL/min/1.73 m². Currently SGLT2i are approved for use when eGFR is above 30 mL/min/1.73m².

- 6.2.9.4 Proteinuric nephropathy, it is recommended to add a GLP1RA or SGLT2i proven to decrease proteinuria GLP1RAs and SGLT2 inhibitors decrease new onset and progression of proteinuria in people with diabetes.
- 6.2.9.5 Weight loss is the main aim, it is recommended to add GLP1RA or SGLT2 inhibitor. GLP1RAs and SGLT2 inhibitors reduce body weight. Effects are comparable. Combination offers greater weight loss than either one alone.
- 6.2.9.6 Hypoglycaemia is the main concern; it is recommended to add SGLT2i or GLP1RA or DPP4i or pioglitazone. Hypoglycaemia is less with SGLT2i, DPP4i, pioglitazone and GLP1RAs compared to insulin or sulfonylurea. Above four classes of drugs have minimal risk of inducing hypoglycaemia in people with T2DM.
See 6.3 for specific considerations on using SGLT2i and GLP1RAs
- 6.2.10 In a setting where resources are limited and / or cost is a major limitation, decide on suitable add-on therapy after considering risk of hypoglycaemia, weight gain, ASCVD, renal disease and glucose lowering efficacy. Hypoglycaemia is associated with increased risk of cardiovascular events and mortality. Weight gain is a risk factor for cardiovascular events, deteriorating glycaemic control and other obesity related complications. When ASCVD, renal disease or risk factors are present, glucose lowering agents with beneficial effects or, at least no harm should be selected.
- 6.2.11 In a setting where resources are limited and or cost is a major limitation and hypoglycaemia is a major concern,
- 6.2.11.1 It is recommended to add DPP4i or pioglitazone, or acarbose
 - 6.2.11.2 Gliclazide may be considered if DPP4i, pioglitazone and acarbose are not available or not tolerated
 - 6.2.11.3 It is recommended to minimize sulfonylurea
 - 6.2.11.4 In the absence of definite indications for insulin, it is recommended to minimize short or rapid acting insulin
 - DPP4i, pioglitazone and acarbose do not increase the risk of hypoglycaemia.
 - As a class, sulfonylureas are associated with increased risk of hypoglycaemia. Among sulfonylureas, gliclazide has a relatively lower risk of hypoglycaemia and glibenclamide has a relatively higher risk of hypoglycaemia.
 - Insulin is associated with increased risk of hypoglycaemia. Risk is highest with short or rapid acting preparations.
- 6.2.12 In a setting where resources are limited and or cost is a major limitation and weight gain is a major concern,
- 6.2.12.1 Addition of DPP4i or acarbose is recommended.
 - 6.2.12.2 Addition of modified release gliclazide may be reasonable
 - 6.2.12.3 It is recommended to minimize the use of other sulfonylureas and pioglitazone
 - 6.2.12.4 In the absence of definite indications, it is recommended to minimize the use of short or rapid acting insulin

- DPP4is are weight neutral. Acarbose is weight neutral or may cause a mild weight reduction specially when used in combination with insulinotropic agents and in obese individuals. Disturbing gastrointestinal adverse effects and frequent dosing schedules may limit its use.
- Modified release gliclazide causes less weight gain than other sulfonylureas during long term use. Insulins and sulfonylureas cause weight gain.

6.2.13 In a setting where resources are limited and / or cost is a major limitation and presence or high risk of ASCVD is the major concern,

- 6.2.13.1 It is reasonable to add modified release gliclazide or pioglitazone or DPP4i
- 6.2.13.2 It may be reasonable to add acarbose
- 6.2.13.3 If heart failure is present, avoid pioglitazone and saxagliptin
- Modified release gliclazide has shown no increase in cardiovascular events and/or mortality. Among sulfonylureas, gliclazide and glimepiride are associated with lower all-cause and cardiovascular mortality.
- DPP4i have a neutral effect on cardiovascular events, heart failure and mortality. Saxagliptin showed an increased risk of hospitalization for heart failure
- Pioglitazone reduces cardiovascular events in people with established cardiovascular disease, but increases the risk of hospitalizations for heart failure.
- Acarbose has a neutral effect on cardiovascular outcomes.

6.2.14 In a setting where resources are limited and or cost is a major limitation and presence or high risk of CKD is the major concern,

- 6.2.14.1 It is reasonable to add a non-renally excreted DPP4i linagliptin
- 6.2.14.2 It may be reasonable to add other DPP4i with appropriate dose adjustment or acarbose or sulfonylurea with lower risk of hypoglycaemia such as gliclazide or glimepiride
- 6.2.14.3 Metformin should be continued in the usual dose until GFR in less than 45 mL/min/1.72m² and dose should be reduced to 1g per day when GFR is 30-45 mL/min/1.72m²
- 6.2.14.4 Metformin should not be continued if GFR is less than 30
- 6.2.14.5 DPP4i are not recommended for use in stage V CKD
- 6.2.14.6
- Use of sulfonylureas is associated with increased risk of hypoglycaemia in people with CKD. However, risk is less with SUs having inactive metabolites like gliclazide and glimepiride. SUs have not shown nephroprotective effects independent of glycaemic control.
- DPP4is have no impact on renal function. DPP4i may delay the onset and retard the progression of albuminuria. However, it is not known whether this is a class effect. In stage III and IV kidney disease, DPP4is except linagliptin require dose adjustment. None of the DPP4i has been used in stage V CKD, in large scale clinical trials.

- Acarbose may be used in any stage of CKD without adverse cardiovascular, renal or hepatic effects. It may have cardiovascular protective effects according to a retrospective real-world study among CKD patients. Its use may be limited by gastrointestinal adverse effects.
- Pioglitazone may reduce albuminuria but does not alter the progression of CKD. Fluid retention may limit the use of pioglitazone among patients with CKD.

6.3 Insulin therapy

Patient with T2DM may require insulin in the following circumstances

- Oral hypoglycaemic failure (inability to achieve desired target glucose control despite adequate doses of oral glucose lowering therapies with good adherence to lifestyle and pharmacological interventions)
- At the time of diagnosis if insulinopaenic features (weight loss, polyuria) with severe hyperglycaemia ($\text{HbA1c} > 10\%$) are present.
- Advance disease with beta cell failure (severe hyperglycaemia and insulinopaenic features)
- Acute illness requiring hospital admission
- Pregnancy

Insulin requirement is temporary in the last two instances. After resolution of the acute illness and after end of the pregnancy, the patient can return to his/her pre-morbid / pre-pregnancy noninsulin-based treatment, guided by the glycaemic status.

6.3.1 The following insulin regimens can be used as appropriate

6.3.1.1 Basal insulin only: Long-acting insulin analogue or intermediate acting human insulin (once or twice a day). This is appropriate when glycaemic status is above target but has no features of insulinopaenia. This is a preferred regime for insulin initiation.

6.3.1.2 Basal and single bolus (basal plus): long-acting insulin analogue or intermediate acting human insulin with single dose of short acting human insulin or rapid acting insulin analogue. This is appropriate when basal only regimen fails to control postprandial hyperglycaemia with a marked postprandial increase after the largest meal of the day

6.3.1.3 Twice daily premixed insulin: provides a combination of intermediate acting and short or rapid acting insulins in a fixed dose ratio. This provides the convenience of infrequent dosing, but titration of doses is difficult due to the fixed ratio of combination. It is suitable as an intermediate option or an alternative to basal bolus regimen.

6.3.1.4 Basal bolus regimen: long-acting insulin analogue or intermediate acting human insulin once or twice a day, with multiple (usually 3) boluses of short acting human insulin or rapid acting analogues to provide prandial insulin requirement before the main meals. This is suitable as the step-up strategy when basal only or basal and single bolus regimen fails or when having insulinopaenic features. It is also the preferred regimen during pregnancy if insulin is required.

- Long-acting analogues may be considered over intermediate acting human insulin if frequent hypoglycaemia occurs with the latter
- Rapid acting analogues may be considered over short acting human insulin if frequent hypoglycaemia occurs before the next meal with the latter insulin
- Patient and caregiver should be adequately educated and trained on insulin storage, administration, recognition and management of hypoglycaemia

Type 2 Diabetes mellitus

Metformin as first line combined with comprehensive lifestyle modification

Assess need for second agent

- For initial dual therapy if HbA1c 8-10% percentage points /above target.
- If HbA1c > 10%, add insulin
- As add-on therapy if HbA1c is above target
- Compelling indication for cardiorenal protection
- As an alternative if metformin is contraindicated / not tolerated

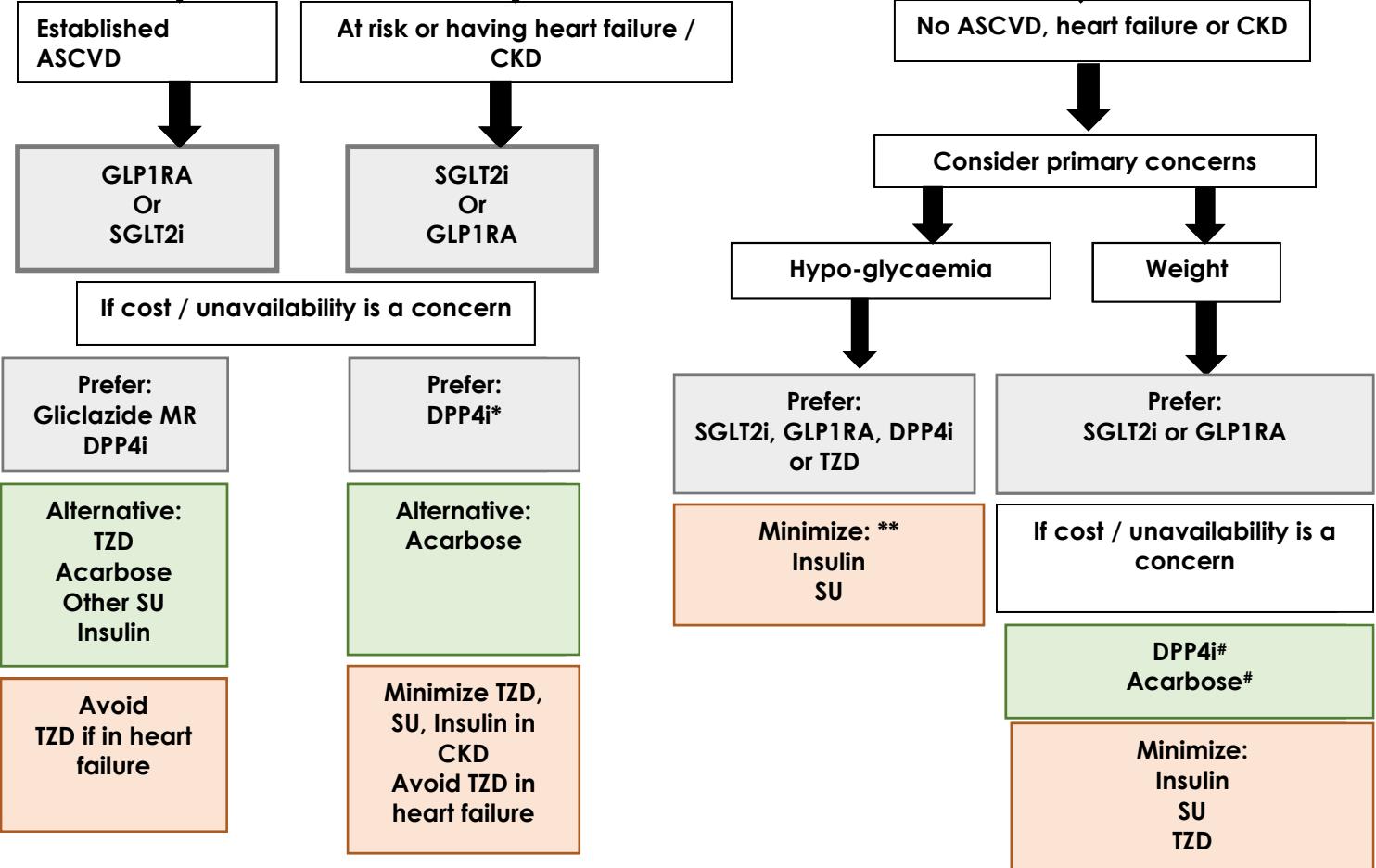


Figure6.3: Choice of pharmacotherapy in people with T2DM opting for glycemic control centered strategy

* Where necessary adjust the dose according to stage of CKD. Avoid DDP4i in stage V CKD. Avoid saxagliptin in heart failure, consider using newer generation slow-release sulfonylureas or basal insulin analogues.

Does not cause weight loss

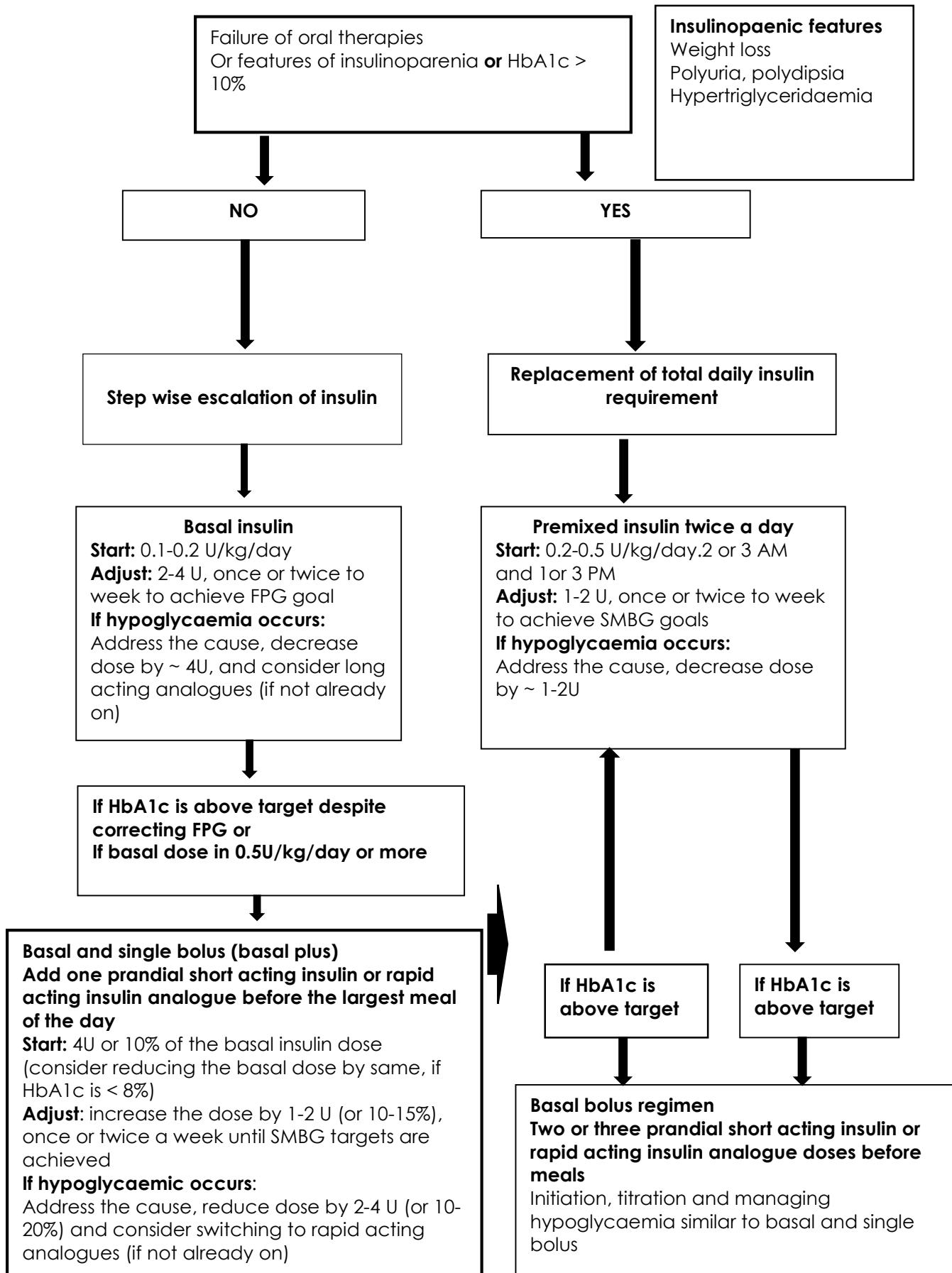


Figure 6. 4: Initiation and intensification of Insulin

6.4 Diabetes remission

Intensive lifestyle modification with a short term very low-calorie diet, graded exercise and gradual food reintroduction, aiming 15% weight loss and maintenance has been shown to induce remission of T2DM in 2 randomized controlled trials. However, these studies are limited by small sample size. Acceptability of the intervention to local setting and sustainability remain unknown. Where appropriate this may be considered in adults with recently diagnosed T2DM after discussing the above uncertainties.

Patient characteristics where diabetes remission with VLCD may be appropriate:

- Recent onset T2DM
- Obese or overweight
- Absence of features of insulinopaenia - Symptoms of hyperglycaemia, weight loss, very high random plasma glucose or HbA1c > 10%
- Motivated and committed
- Education, adherence
- Cost and availability of medication
- Patient preference

Chapter 7

Management of Type 1 Diabetes Mellitus

7.1. Introduction

Type 1 Diabetes Mellitus (T1DM) accounts for 5-10% of diabetes worldwide and the incidence has been rising approximately 3% per year. T1DM continues to remain a fundamental challenge to the patients, their families and clinicians. This is due to higher rates of diabetes related vascular complications, hospitalization with severe hypoglycaemia and diabetic ketoacidosis and suboptimal care strategies leading to a rise in healthcare expenditure

7.2. Diagnosis

7.2.1. People with T1DM usually present with symptoms. It is recommended to establish the diagnosis of diabetes mellitus based on glucose criteria.

7.2.2. It is suggested not to use HbA1c as a diagnostic test for T1DM due to the rapid onset of the disease course.

7.2.3. It is suggested to consider clinical grounds in adults presenting with hyperglycemia to differentiate T1DM from other types. People with T1DM typically (but not always) have one or more of following:

- Ketosis (Blood ketones > 3mmol/L or Urine ketones 2+)
- Age of onset below 35 years
- Rapid weight loss
- BMI below 23* kg/m²
- Personal and/or family history of autoimmune disease
- Failure to respond to oral therapy

(*Using Asian cutoffs for BMI)

Do not disregard the diagnosis of T1DM if an adult presents with a BMI of 23 kg/m² or above or is aged 35 years or above

7.2.4. It is recommended that all patients with clinically suspected T1DM should be referred to a specialist team (specialist physician in Internal medicine/endocrinologist) for confirming the diagnosis and deciding on a care plan.

7.2.5. It is recommended to consider the measurement of pancreatic autoantibodies or c-peptide levels when the clinical diagnosis of T1DM is uncertain i.e.: BMI > 23kg/m², slow evolution of hyperglycemia, slow prodrome, absence of ketosis, strong family history suggesting monogenic form of diabetes, presence of features of insulin resistance.

Autoantibodies in T1DM:

- Five autoantibodies can be tested:
 - Glutamic acid decarboxylase autoantibodies (GAD65)
 - Islet cell cytoplasmic autoantibodies (ICA)
 - Insulin antibodies (IAA)
 - Protein tyrosine phosphatase antibodies (ICA512 or IA2A)
 - Zinc transporter protein (ZnT8)
- Use of two different pancreatic autoantibody tests increase the diagnostic accuracy.
- Pancreatic autoantibodies are present at the time of diagnosis in 85-95% of people, but the antibody titre declines with time, therefore, it is important to measure antibodies soon after diagnosis if there is doubt.
- Antibody negativity does not exclude the diagnosis of T1DM in patients with high clinical pretest probability as up to 20% will be negative at diagnosis.

Role of C-peptide measurement:

- In the established T1DM, C peptides levels would be undetectable or very low. However, during the initial 2 years after the diagnosis (honeymoon period), C-peptide levels could be measurable in some patients, thus detectable levels during this period would not exclude T1DM.
- Do not test C Peptide during hyperglycemic crisis/Diabetic ketoacidosis (DKA): allow at least 2 weeks gap between the normalization of hyperglycemia and C-peptide measurement as hyperglycemic crisis may result in falsely low C-peptide levels.
- Interpretation:
 - C-peptide level < 0.2 nmol/L (0.6ng/mL) while the random glucose level is >200mg/dL suggests severe insulin deficiency and warrants treatment with insulin.
 - C-peptide level > 0.6 nmol/L (1.8ng/mL) with diabetes duration more than 2 years confirms substantial endogenous insulin secretion and T1DM is less likely.
 - C-peptide level of 0.2 – 0.6 nmol/L (0.6 -1.8 ng/mL): likely to be T1DM if done early during disease course or T2DM of long-standing duration.

7.2.6. It is suggested to include all T1DM patients into a dedicated type 1 registry.

7.2.7. Associated autoimmune disease screening is recommended in all patients with T1DM, with TSH measurement at diagnosis and annually. Other relevant screening (for Coeliac screening, Addison's disease, Pernicious anemia) should be considered when there is a clinical suspicion.

7.2.8. Routine screening for family members of a patient with T1DM is not recommended.

7.3. Immediate Management

- 7.3.1. All newly diagnosed T1DM if they have symptoms and signs of ketoacidosis (DKA), It is recommended to admit and test for blood or urine ketone bodies and manage appropriately (see Section 14)
- 7.3.2. People without features of DKA, it is recommended to commence on insulin in the out-patient setting but should be referred to a T1DM specialist team for ongoing care
- 7.3.3. It is recommended to commence treatment with insulin on all patients with T1DM at the diagnosis (see section on Treatment 7.6.)

7.4. Early Care Plan

7.4.1. Early care plan for patients with T1DM should include:

- Individual education on diabetes from a healthcare professional trained to manage T1DM including basic carbohydrate counting, insulin management, hypoglycaemia and sick day rules
- Individual nutritional advice
- Advice on physical activity including blood glucose targets pre/post exercise and management of hypo/hyperglycemia
- Invitation to a structured training course in T1DM within 6-12 months of diagnosis to enhance self-management of T1DM
- Access to psychological support when required
- Ongoing support for self-management from a multidisciplinary team (specialist Physician, DENO, nutritionist, etc.)
- An individualized care plan outlining what care to be expected with treatment targets and annual care process

7.5. Blood glucose monitoring and glycemic goals

7.5.1. HbA1c measurement

7.5.1.1. It is recommended to measure HbA1c levels every 3–6 months in adults with T1DM

7.5.1.2. Target HbA1c should be 6.5-7% but target should be personalized taking account to individual preference, age, frailty, comorbidities and history of severe hypoglycaemia.

7.5.2. Self-Monitoring of Blood Glucose (SMBG)

7.5.2.1. It is recommended to educate adults with T1DM about how to measure their blood glucose level, interpret the results and take necessary action. Review these skills at least annually

7.5.2.2. It is recommended to advise routine self-monitoring of blood glucose levels for all adults with T1DM according to an individualized plan, perform testing at least 4 times a day (before each meal and before bedtime). Frequently monitoring leads to improved HbA1C levels ⁽¹²⁾

7.5.2.3. Recommended targets for SMBG are as follows:

- On waking – 90 -126 mg/dL (5-7 mmol/L)
- Pre-prandial – 72 – 126 mg/dL (4 – 7 mmol/L)
- Post-prandial – 90 – 160 mg/dL mg/dL (5 – 9 mmol/L)
- Before bed – 140 – 180 mg/dL (individualized bedtime target plasma glucose levels should be adjusted according to the fasting level on waking)

7.6. Treatment

7.6.1. Insulin regime

7.6.1.1. It is suggested to adapt the insulin regimen to the individual's needs taking into account age, dependency and the relative risks of hyper and hypoglycaemia

7.6.1.2. It is recommended to use multiple daily injection (MDI) basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the regimen of choice for all adults with T1DM.

7.6.1.3. It is suggested that twice daily pre-mixed insulin may be offered ONLY for those who are unable to use a basal bolus regimen

7.6.1.4. Patients who fulfill certain criteria will benefit continuous subcutaneous insulin injection (CSII) after initial basal bolus regime.

7.6.2. Long-acting insulin

7.6.2.1. Once a day insulin glargine / insulin degludec or twice a day insulin detemir is recommended as the preferred long acting (basal) insulin for patients with T1DM

7.6.2.2. In the event of unavailability of basal long-acting insulin, it is suggested twice a day intermediate acting insulin (NPH/isophane insulin) as a substitution to long-acting insulin

7.6.3. Short/Rapid acting insulin

7.6.3.1. It is recommended to offer short-acting human insulin or rapid-acting analogue insulin to be injected before meals.

7.6.3.2. It is recommended to teach individuals to match bolus insulin doses to carbohydrate intake (through carb counting and insulin to carb ratio [ICR]), adjusted for pre-meal blood glucose and planned activity)

7.6.3.3. In individuals who are not carb-counting, it is suggested to use a fixed dose short acting/rapid acting insulin before meals according to the blood glucose monitoring.

7.6.3.4. Provision of education is recommended for the management of insulin dosages in MDI during specific circumstances e.g., exercise, sickness, and steroid therapy.

7.6.4. Pre-mixed insulin

- 7.6.4.1. Individuals using a pre-mixed insulin should be taught how to maintain a fixed dietary regimen and how to exchange food for fixed carbohydrate intake (carb-exchange) to match their insulin dose.
- 7.6.4.2. Addition of a mid-day meal-time short-acting insulin to the pre-mixed insulin twice-daily regime is suggested when the glycemic targets are not achieved with optimization of premixed insulin regime and dietary modifications.

7.6.5. Adjuncts

- 7.6.5.1. It is suggested to consider adding metformin to insulin therapy if an adult with T1DM and a BMI of 23 kg/m² or above wants to improve their blood glucose control while minimizing their effective insulin dose.
- 7.6.5.2. Use of SGLT2i in T1DM is not recommended due to the risk of serious side effects including DKA.

7.7. Transitional care in T1DM

- 7.7.1. It is recommended to establish a formal process of transition, to include well planned joint transition clinics with a pediatric and an adult T1DM caring physicians, in every specialized unit
 - Staff working in transition and young adult clinics should be trained in good communication skills relevant to young people
 - Special consideration should be focused on physical, psychological, and social changes during transitional age, including pubertal changes, increased body weight and insulin resistance, changes in eating patterns and physical activities, psychological pressures, social interactions, peer group influences.
 - Psychological support should be available to adults undergoing transition of care
- 7.7.2. It is recommended to audit the attendance rates and outcomes during transition of T1DM care

7.8. Follow-up consultations and long-term care

7.8.1 It is recommended the specialist teams to provide individualized continuity of care and consultations.

7.8.2. It is recommended that every consultation to focus on holistic management of T1DM including:

- Positive reinforcement and recognition of what the individual has already achieved with glycemic control
- Achieving / maintenance of glycemic targets (HbA1c/ SMBG)
- Reinforcing insulin delivery systems and dosages
- Recognition and prevention of DKA
- Assessment of incidence of hypoglycaemia/ awareness and management and revision of sick day rules
- Discussion on current complications
- Effect on daily activities (Sports, Exercise, eating out etc.)
- Identifying psychological issues
- Identification of areas where further education would be beneficial
- Identification of potential for use of technology (Smart glucose meters, Bolus calculators, Flash glucose monitoring, Continuous Glucose Monitoring, Continuous subcutaneous insulin injection – CSII or Artificial pancreas) or potential surgery (pancreatic transplant).

7.8.3. It is recommended routine checks for diabetes related complications to be carried out annually and care planning should be adjusted accordingly.

7.8.4. It is recommended to review the care plan at least annually and referral for specialist review should be considered as required (e.g., nephrology, podiatry, cardiology, ophthalmology)

Chapter 8

MANAGEMENT OF DIABETES SECONDARY TO PANCREATITIS

8.1 Introduction

- Type 3c diabetes (also known as pancreatogenic diabetes) is diabetes that comes secondary to pancreatic diseases, involving the exocrine and digestive functions of the pancreas.
- People with chronic pancreatitis have a greatly increased risk of developing diabetes, with a lifetime risk as high as 80%. The risk increases with duration of pancreatitis and presence of calcific pancreatitis.

Recommendations

8.1.1 Screening for pancreatogenic diabetes

Assess people with chronic pancreatitis and pancreatic disease for the presence of pancreatogenic diabetes every 6 months.

8.1.2 Diagnosis of pancreatogenic diabetes

Though, there are no universally accepted criteria for the diagnosis of pancreatogenic diabetes, the diagnosis can be made in patients who meet the following three prerequisites: who fulfill the diagnosis of diabetes, who have a disease of exocrine pancreas, and whose diabetes is reasonably certain to be secondary to the disease of exocrine pancreas.

Only available diagnostic guidelines devised by "Ewald and Hardt" suggest major and minor criteria to aid the diagnosis of pancreatogenic diabetes and to differentiate from T1DM & T2DM.

Major criteria - all must be present:

- I. Pancreatic exocrine insufficiency
- II. Pathological pancreatic imaging
- III. Absence of T1DM associated autoantibodies

Minor criteria include: absent pancreatic polypeptide secretion, absence of insulin resistance, impaired beta cell function and low serum levels of fat soluble vitamins.

8.1.3 Management of pancreatogenic diabetes

8.1.3.1. Management should be done with a multi-disciplinary team involving a specialist physician, endocrinologist, gastroenterologist, clinical nutritionist and DENO.

8.1.3.2 Lifestyle modifications:

- Abstaining from alcohol and smoking cessation to reduce the toxic and modifiable contributors for pancreatic damage is recommended.
- Well-balanced diet which is rich in soluble fibre and low in fat together with oral pancreatic enzyme replacement and fat-soluble vitamins in needed patients is recommended.

8.1.3.3 Anti-hyperglycaemic agents:

- Metformin or insulin is used as first-line therapy, and their use might be tailored to the specific presentation of the patient. The role of other anti-diabetic agents is unclear.
- Early during diabetes, particularly if hyperglycaemia is mild ($\text{HbA}_{1c} < 8\%$ or $< 64 \text{ mmol/mol}$), metformin alone might be considered as a first-line agent.
- In advanced diabetes, Insulin therapy is recommended as it addresses the associated insulin deficiency.
- However, there is a risk of hypoglycaemia with insulin therapy, particularly in patients with chronic pancreatitis who might have enhanced peripheral insulin sensitivity.
- In advanced disease, multi-dose basal-bolus insulin dosing and regimens should follow guidelines for the treatment of T1DM, and include carbohydrate counting for flexible prandial coverage and consideration of continuous subcutaneous insulin infusion or 'pump' delivery.
- The incretin-based therapies—injectable GLP-1 analogues and oral DPP-4 inhibitors—are typically avoided in chronic pancreatitis because of their potential role in increasing risk for acute pancreatitis and pancreatic ductal adenocarcinoma.
- The thiazolidinediones increase both hepatic and peripheral insulin sensitivity but carry an increased risk of bone fracture, so their use might not be well suited for patients who are already at increased risk for this complication.
- Total pancreatectomy with islet auto transplantation (TPIAT) which is considered in highly selected patients to treat severe complications, e.g., intractable pain of recurrent acute/chronic pancreatitis or a very high risk of pancreatic cancer, may increase the chance of good glycaemic control.

8.2 STEROID INDUCED DIABETES

8.2.1 Introduction

Steroid-induced diabetes mellitus is defined as an abnormal increase in blood glucose associated with the use of glucocorticoids in a patient with or without a prior history of diabetes mellitus.

The mechanism by which glucocorticoids cause hyperglycaemia is multifactorial, including augmentation of hepatic gluconeogenesis, inhibition of glucose uptake in adipose tissue and alteration of receptor and post receptor functions.

8.2.2. Patients with no known Diabetes

Recommendations

Check HbA_{1c} prior to the commencement of steroids in patients perceived to be at high risk.

It is recommended to monitor blood glucose at commencement of steroid, recommend capillary blood glucose (CBG) once daily pre or post lunch or evening meal, in those at 'high risk' or with symptoms suggestive of 'hyperglycaemia'.

- Blood glucose target would be CBG 110-180 mg/dL with 70-220 mg/dL being an acceptable level. In patients on end-of-life care, target would be 110-270 mg/dL.

- If CBG consistently <180 mg/dL on repeated testing on multiple days, consider cessation of CBG testing.
- If the CBG is below 220 mg/dL consider the patient to be at low risk and record the CBG daily post breakfast or post lunch.
- If CBG is found to be greater than 220 mg/dL, the frequency of testing should be increased to four times a day.

If a capillary blood glucose is found to be consistently greater than 220 mg/dL (i.e., on 2 occasions or more during a 24-hour period) then the patient should enter the treatment **algorithm** below.

Box 8.1

CBG readings above desired target (110-180 mg/dL- acceptable range 70-220 mg/dL)
Add in Gliclazide 40 mg with breakfast and increase the dose by 40 mg increments daily if targets are not reached



If target is not achieved and no symptoms of hypoglycaemia are experienced by the patient despite being on 160 mg of Gliclazide in the morning, consider titration to 240 mg in the morning



If still no improvement on maximum dosage, consider:

Adding an evening dose of Gliclazide or add morning intermediate acting NPH insulin
e.g., Humulin I/Insulatard/Insuman basal

For NPH – commence 10 units daily in the morning and titrate every 24 hours by 10-20% to achieve desired CBG target



1. Monitoring will need to be continued in patients remaining on glucocorticoids post-discharge
2. If steroid treatment is ceased in hospital and hyperglycaemia has resolved CBG can be discontinued post discharge
3. If steroids are discontinued prior to discharge and hyperglycaemia persists then continue with monitoring until
 - Normoglycaemia is achieved OR
 - A definitive test for diabetes is undertaken (FBS/HbA1C/OGTT).
4. Consider continuing previous treatment with adjusted doses

8.2.3 Guidance for patients with T2DM on Steroid therapy

Recommendations

1. Refresh diabetes education to patient
2. Recommend CBG testing four times a day (pre-meal and before-bed time)
3. Target for capillary blood glucose e.g., 110-180 mg/dL with 70-220 mg/dL being acceptable. If CBG is more than 220 mg/dL, consider up-titrating as follows:

If hyperglycaemia on non-Insulin therapies:

- Gliclazide – titrate to maximum of 320 mg daily, with maximum of 240 mg in the morning
- Metformin – titrate to maximum of 1g BD
- Pioglitazone could be considered but other agents have limited evidence in treating steroid induced hyperglycaemia

If above measures fail, consider basal Insulin: Starting dose 10 units in the morning and up titrate by 4 units or 10-20% till targets achieved.

If hyperglycaemia on Insulin therapies:

- If on evening once daily human Insulin, consider switch to morning dosing:
 - Increase dose by 10-20% daily depending on pre-evening meal CBG levels
 - If targets not achieved consider twice daily Insulin or basal bolus regime
- If uncontrolled hyperglycaemia on twice daily Insulin:
 - Consider increasing morning dose by 10-20% daily depending on pre-evening meal CBG level
 - If targets not achieved, consider basal bolus Insulin
- If uncontrolled hyperglycaemia on multiple daily doses of Insulin, switch to basal analogue Insulin (or alternative regimen – Premix/ basal bolus insulin) and involve specialist team in hospital.
- Beware of nocturnal and early morning hypoglycaemia

8.2.4 Hospital discharge of patients at high risk of steroid induced diabetes/ hyperglycaemia

Steroids commenced and patient discharged

- Standard education for patient and carer
- Blood glucose testing once daily (pre or post lunch or evening meal)
- If blood glucose reading greater than 220 mg/dL increase the frequency of testing to four times daily
- If two consecutive blood glucose readings greater than 220 mg/dL, follow algorithm for management of steroid induced diabetes

Patient discharged on decreasing dose of steroid above 5 mg/day

- Standard education for patient and carer including advice on hypoglycaemia
- Continue CBG monitoring until blood glucose normalizes (70-126 mmol/L)
- Review by the attending physician (e.g., GP, Specialist physician, endocrinologist etc.) at an appropriate juncture to consider down-titration of antihyperglycaemic therapy if necessary

Patient discharged following steroid cessation

- If hyperglycaemia persists:
 - CBG testing until return to normoglycaemia (4-7 mmol/L) **OR**
 - Until a definitive diagnosis of diabetes is undertaken
- If hyperglycaemia resolved stop CBG testing and arrange definitive test for diabetes:
 - OGTT at 6 weeks
 - HbA1c at 3 months

Chapter 9

Insulin

9.1. Introduction

Insulin therapy is essential for those with T1DM while most with T2DM will need insulin to control blood glucose levels at some point in their lives. Available insulin preparations are recombinant human insulins or their analogues.

Insulins are available as basal or bolus. Basal insulin suppress hepatic glucose production and maintain near-normoglycemia in the fasting state while bolus insulin helps to control post prandial blood glucose surges after food is absorbed.

9.2. Types of insulins available:

9.2.1. Regular/ soluble (short acting) insulin – given about 15 to 30 minutes before meals

- Provide post prandial insulin
- When given subcutaneously - peak action between 1 to 4 hours, duration of action of up to 9 hours
- When given intravenously – onset of action is instantaneous, and the half-life is only a few minutes

9.2.2. NPH (isophane) insulin (intermediate acting)

- Provide basal insulin
- When given subcutaneously
 - Onset of action approximately 1–2 hours
 - Maximal effect at 3–12 hours
 - Has a peak effect that occurs between 4 - 10 hours after dosing
 - Duration of action of 11–24 hours
- Can be mixed with short acting insulins in the same syringe

9.2.3. Pre-mixed (biphasic) insulin (a mixture of both short and intermediate acting insulin in varying proportions)

- Must be administered 15-30 minutes before meals

9.2.4. Long-acting insulins – e.g. protamine zinc insulin, insulin zinc suspension

- Mimic endogenous basal insulin secretion
- Duration of action may last up to 36 hours
 - Achieve a steady-state level after 2–4 days to produce a constant level of insulin

9.2.5. **Recombinant insulin** analogues with desired pharmacokinetic changes

9.2.5.1. **Rapid-acting analogues (RAAs)** – e.g., insulin aspart, insulin glulisine, and insulin lispro. Rapid onset of action, given shortly before meals.

- Routine use after meals should be discouraged. When given during or after meals, are associated with
 - Poorer glucose control
 - An increased risk of high postprandial-glucose concentration and subsequent hypoglycaemia
- Effective in managing postprandial hyperglycaemia
 - Rapid onset (within 15 minutes) and shorter duration of action (2-5 hours)
 - Results in better control of postprandial blood-glucose
 - Less frequent occurrence of post prandial hypoglycaemia (therefore less snacking)
 - Allow for greater flexibility of mealtimes in relation to an active lifestyle.

9.2.5.2. **Long acting (basal) analogues** with slower onset of action which lasts for long periods, e.g., insulin detemir, insulin glargine, and insulin degludec. More similar to endogenous basal insulin secretion than NPH.

- Insulin glargine and insulin degludec - given once daily
- Insulin detemir - given once or twice daily according to individual requirements.
- Provides basal insulin requirements
 - Slow and continuous absorption into systemic circulation
 - Minimal/absent peak activity
 - Prolonged duration of action
- Associated with lower incidence of hypoglycaemia
 - Has the potential to allow larger doses than NPH insulin
 - Would lead to improved fasting glycaemic control, without an increased risk of nocturnal hypoglycaemia
- Cause less weight gain compared to NPH.

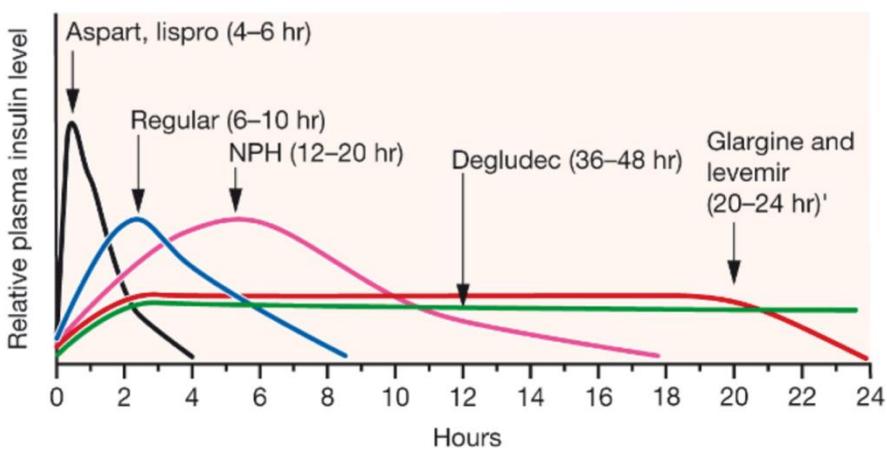


Figure 9.1: Approximate pharmacokinetic profiles of human insulin and insulin analogues

The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons

(From Hirsch I B 2005 Insulin analogues. New England Journal of Medicine 352:174–183.)

Concentrated insulins are currently not available in the Sri Lankan market but may be needed for patients who need very high doses of insulin.

9.3. Insulin regimens

- Intensive insulin therapy with multiple daily injections (or continuous subcutaneous insulin infusion) is recommended to maintain strict glycaemic control in patients with type 1 diabetes. Insulin replacement in patients with type 1 diabetes consists of prandial (bolus) insulin, basal insulin and a correction-dose insulin supplement. The last is given to address pre-meal or between-meal hyperglycaemia, independently of the prandial insulin.
- Due to the progressive nature of type 2 diabetes, many patients will require insulins at some stage for optimal glycaemic control. Basal insulin added to oral therapy will reduce hepatic glucose production that “occur” between meals and limit nocturnal hyperglycaemia. Short acting insulins can be used when there is uncontrolled post prandial hyperglycaemia.

9.3.1. Basal only insulin regimens

- Basal insulin given at night

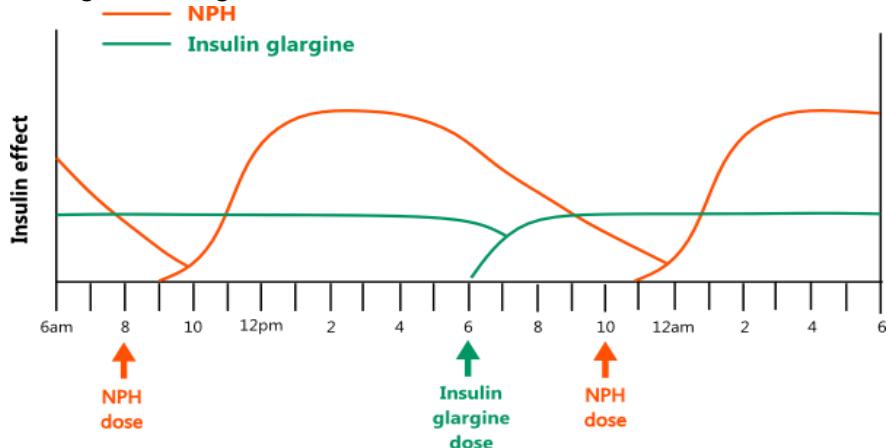


Figure 9. 2: Basal insulin regimen given at night

<https://www.straighthealthcare.com/insulin-dosing.html>

9.3.2. Basal plus regimen

- Basal insulin + 1 mealtime short/rapid acting insulin

9.3.3. Split mixed /pre-mixed insulin regimens

- These are usually given twice a day
- Timing in relation to meals will depend on the type of short acting insulin available. Those containing analogues can be given immediately premeal
- Provides a reasonable blood glucose control with good dose titration

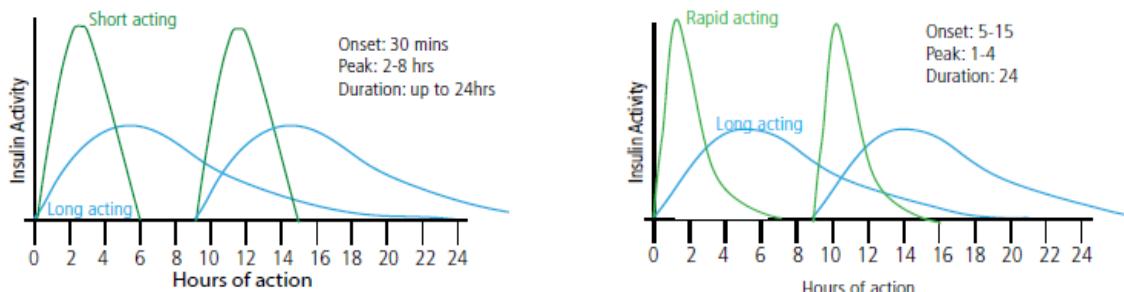


Figure 9.3: Split mixed / pre-mixed insulin regimens

Pre-mixed with regular/soluble insulin pre-mixed with rapid acting insulin analogues
<http://askdis.blogspot.com/2017/10/conversion-novomix-to-mixtard.html>

9.3.4. Premixed plus

- Adding a short acting insulin at lunch time to a premixed regimen

9.3.5. Basal bolus insulin regimens

- Mimic the normal human insulin secretion – gives a better glycaemic control
- Multiple injections of short acting insulin to provide prandial insulin
- The dose of prandial insulin should be according to the type of meal/ amount of carbohydrates in the meal.

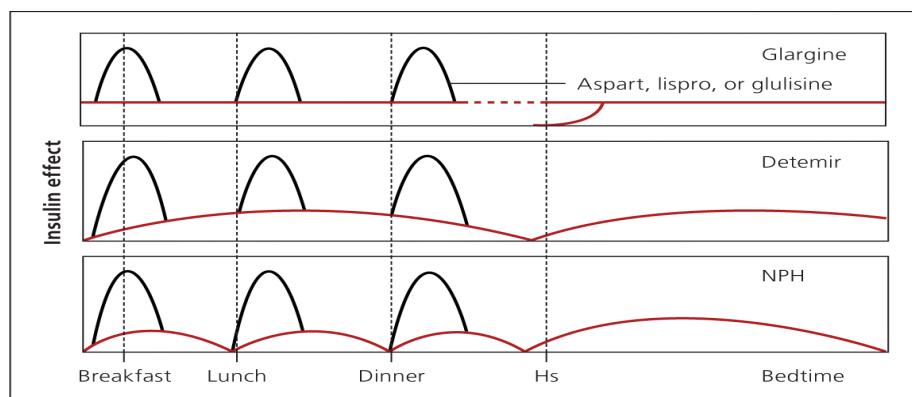


Figure 9.4: Basal bolus insulin regimens

<https://www.aafp.org/afp/2011/0715/p183.html>

9.4. Titrating the dose of insulin

- Before increasing the dose of insulin, assess
 - The dietary control
 - Insulin injection technique
- If the fasting blood glucose not controlled – the nighttime long acting or nighttime basal insulin dose should be increased
- If any post meal blood glucose is not controlled – the dose of prandial insulin given before that meal should be increased
- If both fasting and post meal glucose levels remain high throughout the day – increase all doses of insulin. Alternatively, the regimen might need to be changed.
- Consider “basal-bolus” therapy if glucose targets are not easily achieved with split-mixed regimen.

The high cost is a limiting factor for the use of these newer analogues. However, there is no significant difference in the reduction of HbA1c and glycaemic control achieved with newer analogues compared with the older insulin.

All insulins are given subcutaneously for regular glycaemic control. For acute hyperglycaemic emergencies, regular (short acting) insulin is given intravenously. Both insulin aspart and insulin lispro can be given intravenously as alternatives to soluble insulin for diabetic emergencies and at the time of surgery.

9.5. Common Adverse effects

- Hypoglycaemia is an inevitable adverse effect of insulin treatment, and patients should be advised of the warning signs and actions to take.
 - Any switch between brands or formulation of insulin should be done under strict supervision; may require a change in dose.
- Weight gain
- Local allergy
- Local sepsis
- Lipodystrophy at the injection site

9.6. Biosimilar Insulins (BIs)

Biosimilar insulins (BIs) are available for clinical use and clinicians should be mindful that they are not identical to the reference product and hence not interchangeable. The active substance of a biosimilar medicine is similar, but not identical, to the originator biological medicine. The lower cost compared to recombinant human insulin makes BIs an attractive therapeutic option.

Biosimilar medicines must be prescribed by brand name. The brand name specified on the prescription should be dispensed in order to avoid inadvertent switching. Automatic substitution of brands at the point of dispensing is to be avoided.

Chapter 10

Non-insulin anti-diabetics – oral and injectable

Several classes of non-insulin anti-diabetic drugs are available for management of type 2 diabetes. Some of these are also used as adjunctive therapy in type 1 diabetes. These drugs should be selected based on efficacy, safety, tolerability, patient's comorbidities and concomitant medication. Cost too must be considered, especially when prescription incur an out-of-pocket expense.

10.1. Metformin

- Reduces hepatic glucose production and reduces peripheral insulin resistance
- Has antihyperglycaemic effect, lowers both basal and postprandial blood-glucose concentrations
- Does not stimulate insulin secretion and does not cause hypoglycaemia when given alone
- Both standard release and modified release preparations are available
 - Patients receiving metformin immediate-release may be switched to metformin extended-release once daily at the same total daily dose, up to 2 g once daily
 - As bioavailability of modified release preparations can vary, brand substitution is not recommended
- Dose should be reduced when eGFR is between 45 - 30mL/min/1.73m² and stopped when <30mL/min/1.73m²
- Is used in conjunction with insulin to manage type 1 diabetics, especially if overweight

10.2. Sulfonylureas

E.g., Glibenclamide, Gliclazide, Glimepiride, Glipizide, Tolbutamide

- Stimulate insulin release and can cause hypoglycaemia when given alone
 - More likely with long-acting sulfonylureas such as glibenclamide
 - Severe, prolonged, and sometimes fatal hypoglycaemia can occur
 - Risk is greater if combined with others that stimulate insulin secretion
- Associated with a modest weight gain
 - Glimipride, Gliclazide MR(Modified release), Glipizide ER(extended release) have shown weight neutralizing/ reducing effects
- In those with renal impairment – gliclazide, glipizide or tolbutamide are preferred as they are not renally excreted

10.3. Acarbose

- Inhibits alpha glucosidase in the intestinal brush border
 - Reduces glucose absorption
 - Reduces post prandial hyperglycaemia
- Should be taken before meals

10.4. Thiazolidinediones

E.g., Pioglitazone

- Improves insulin sensitivity and reduces peripheral insulin resistance
- Causes fluid retention
- Causes weight gain
- Increases the fracture risk in females

10.5. Incretin enhancers

E.g., Sitagliptin, Linagliptin, Saxagliptin, Vildagliptin

- Act by inhibiting dipeptidylpeptidase-4 inhibitors
- Do not appear to be associated with weight gain
- Have less incidence of hypoglycaemia

10.6. Incretin mimetics

E.g., Exenatide

- Is a longer acting GLP-1 receptor agonist
- Given as weekly subcutaneous injections
- Known to reduce weight
- Lower risk of hypoglycaemia

** Incretin mimetics and enhancers have been shown to be associated with beneficial effects on cardiovascular risk factors such as weight loss, decrease in blood pressure and changes in lipid profile

10.7. Sodium glucose co-transporter 2 (SGLT-2) inhibitors

E.g., Canagliflozin, Dapagliflozin, Empagliflozin

- Inhibits SGLT-2 cotransporter in proximal renal tubule and reduce glucose reabsorption
- Increases urinary glucose excretion
 - May increase urinary tract infections and genital candidiasis
- Does not induce hypoglycaemia
- Promotes weight loss by increased glycosuria
- Associated with an increased risk of diabetic ketoacidosis
- Reduces the risk of heart failure (HF) hospitalization in adults with type 2 diabetes mellitus (most without prior HF)
 - SGLT2 inhibitor are included among the secondary therapies for HFrEF in patients with type 2 diabetes

Chapter 11

Management of cardiovascular risk factors in diabetes

11.1 Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality for individuals with diabetes. Diabetes is a strong risk factor for ASCVD and confers a two-fold excess risk of vascular outcomes (coronary heart disease, ischaemic stroke, and vascular deaths), independent of other risk factors. The excess relative risk of vascular events with DM was greater in women and at younger ages. In addition, the common conditions associated with T2DM such as hypertension, dyslipidemia also increase the risk of developing ASCVD.

Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes.

11.2 Identifying and assessing cardiovascular disease (CVD) risk

11.2.1. Assessment of cardiovascular risk factors

Following cardiovascular risk factors should be systematically assessed at least annually in all patients with diabetes.

- Obesity/overweight
- Hypertension
- Dyslipidemia
- Smoking
- A family history of premature coronary disease
- Chronic kidney disease/ the presence of albuminuria.

Modifiable abnormal risk factors should be treated as described in this guideline.

11.2.2 Determining CVD Event Risk

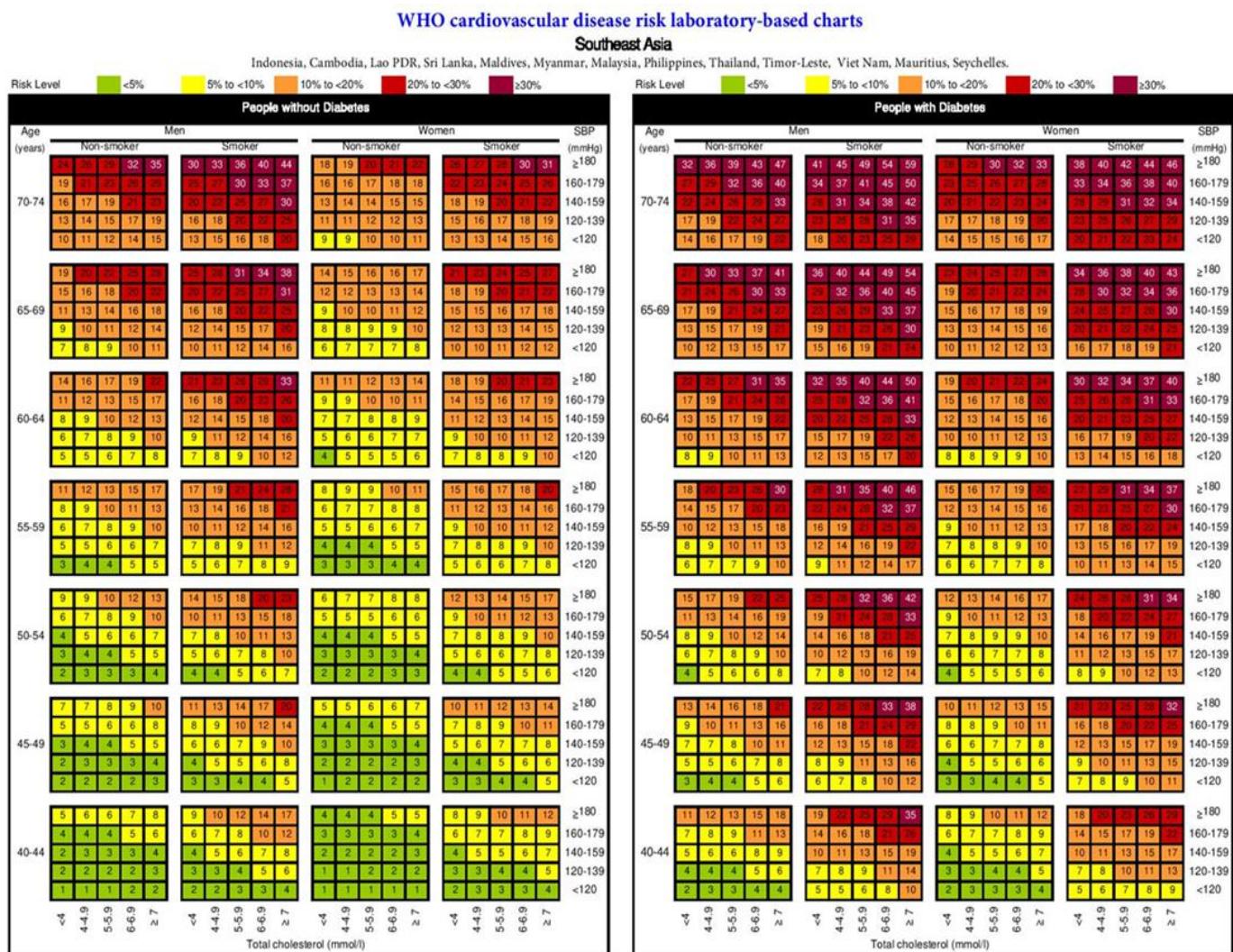
Future cardiovascular risk in individuals with diabetes can be categorized into the following risk levels.

Table 11. 1: Determining CVD events risk

Very high risk	<ul style="list-style-type: none">• Patients with DM and established CVD• or other target organ damage (Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy)• or three or more major risk factors ((Age, hypertension, dyslipidemia, smoking, obesity)• or early onset T1DM of long duration (>20 years)
High risk	<ul style="list-style-type: none">• Patients with DM duration > 10 years without target organ damage plus any other additional risk factor
Moderate risk	<ul style="list-style-type: none">• Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

Future Cardiovascular (CVD) risk of an individual with DM can be calculated based on the cardiovascular risk assessment tools/charts. World Health organization/ International Society of Hypertension (WH0/ISH) risk prediction chart for Sri Lanka is recommended to assess the 10-year risk of a fatal or non-fatal major cardiovascular event (myocardial infarction or stroke), according to age, sex, blood pressure, smoking status, total blood cholesterol.

WHO cardiovascular disease risk laboratory-based charts for Southeast Asia Indonesia, Cambodia, Lao PDR, Sri Lanka, Maldives, Myanmar, Malaysia, Philippines, Thailand, Timor-Leste, Viet Nam, Mauritius, Seychelles.

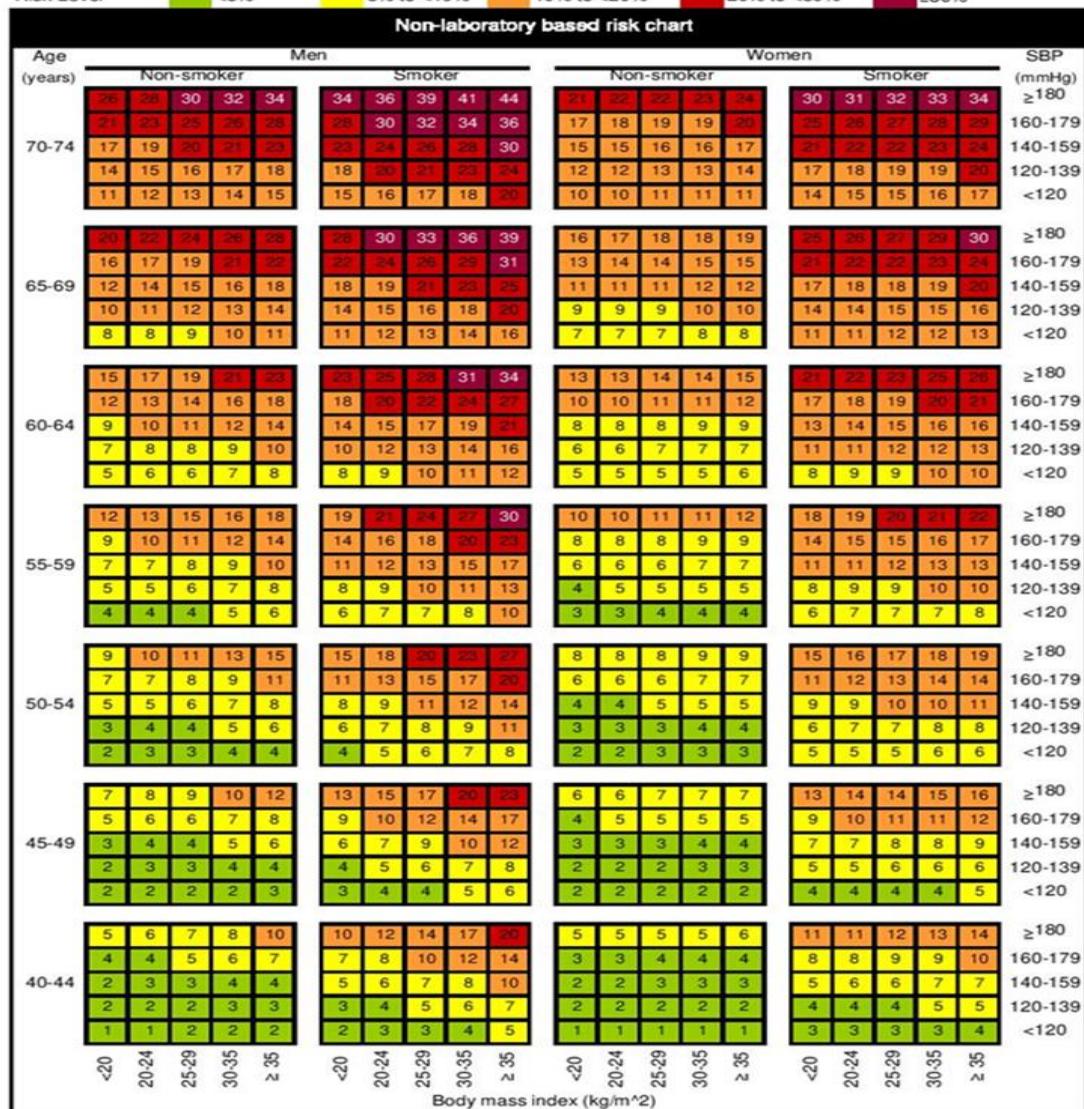


WHO cardiovascular disease risk non-laboratory-based charts

Southeast Asia

Indonesia, Cambodia, Lao PDR, Sri Lanka, Maldives, Myanmar, Malaysia, Philippines, Thailand, Timor-Leste, Viet Nam, Mauritius, Seychelles.

Risk Level <5% 5% to <10% 10% to <20% 20% to <30% ≥30%



Southeast Asia

- **Estimate the 10 year cardiovascular risk as follows using laboratory based charts;**
Step 1 – Select the appropriate chart depending on the presence or absence of diabetes
Step 2 – Select male or female tables
Step 3 – Select smoker or non-smoker boxes
Step 4 – Select age group box (if age is 54; select 50-54, if age is 55; select 55-59)
Step 5 – Within this box find the nearest cell where the individual's systolic blood pressure (mmHg) and the total blood cholesterol level (mmol/l) cross. The colour and the number of this cell determines the 10 year cardiovascular risk.
- **Estimate the 10 year cardiovascular risk as follows using non laboratory based charts;**
Step 1 – Select male or female tables
Step 2 – Select smoker or non-smoker boxes
Step 3 – Select age group box
Step 4 – Within this box find the nearest cell where the individual's systolic blood pressure (mmHg) and the Body Mass Index (kg/m^2) value cross. The colour and the number of this cell determines the 10 year cardiovascular risk.

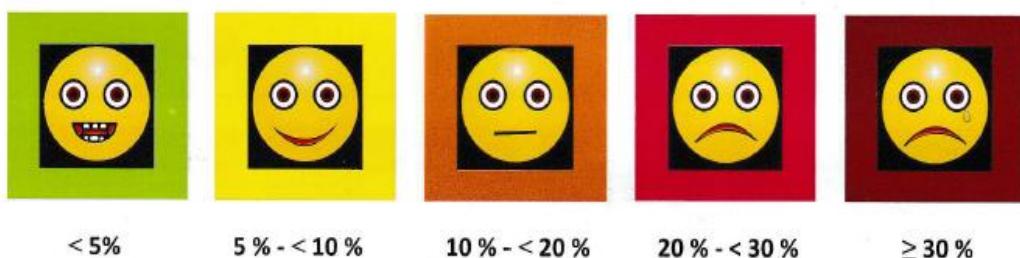


Figure 11. 1: WHO/ISH risk prediction Chart

11.3. Screening for presence of cardiovascular disease

11.3.1. Resting ECG

A resting ECG may detect silent MI in 4% of individuals with DM, which has been associated with increased risk of CVD.

A resting ECG, repeated every 3 to 5 years, should be performed in individuals with diabetes with any of the following [Grade C, Consensus for all the following]:

1. Age >40 years
2. Duration of diabetes >15 years and age >30 years
3. End organ damage (microvascular, CV)
4. ≥ 1 CVD risk factor(s) (current smoking, hypertension, family history of premature CVD in first degree relative [men <55 years, women <65 years], CKD, obesity [$\text{BMI} >30 \text{ kg/m}^2$], erectile dysfunction)
5. Age >40 years and planning to undertake very vigorous or prolonged exercise, such as competitive running, long-distance running or high-intensity interval training

11.3.2. Exercise ECG stress testing

Exercise ECG stress testing should be performed as the initial test when investigating CAD in individuals with diabetes with suggestive cardiac symptoms (chest pain, exertional dyspnea). [Grade C, Consensus]. However, in asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated.

11.3.3. Pharmacological stress echocardiography or nuclear imaging

This should be used in individuals with diabetes in whom resting ECG abnormalities preclude the use of exercise ECG stress testing (e.g., left bundle branch block or ST-T abnormalities).

11.4. Prevention of cardiovascular disease in patients with diabetes and pre-diabetes

11.4.1 Lifestyle modification

- **Smoking cessation**

In individuals with diabetes, smoking is an independent risk factor for all-cause mortality. It increases the risk of MI 1.4-fold, stroke by 30% and progression to end stage renal disease (ESRD); and is associated with poorer glycemic control. Quitting smoking has been shown to reduce CV risk in people with diabetes.

Recommendation

- Smoking cessation guided by structured advice is recommended in all individuals with DM and pre-DM.

- **Weight loss, increased physical activities and medical nutrition therapy**

Even though there is no direct evidence of benefits of intense lifestyle interventions on the CV mortality there is observed benefit on glycemic control. Furthermore, lifestyle intervention, including weight loss, increased physical activity, and medical nutrition therapy, allows some patients to reduce ASCVD risk factors. Therefore, nutrition intervention tailored to patient's age, diabetes type, pharmacologic treatment, lipid levels, and medical conditions is appropriate as a measure to reduce CVD risk factors among patients with DM.

Recommendation

- Lifestyle modification including weight loss if indicated, adopting a Mediterranean style diet or Dietary Approaches to Stop Hypertension (DASH) eating pattern, reduction of saturated fat and *trans*-fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake is recommended to improve the lipid profile and reduce the future risk of developing CVD in patients with DM.

- **Moderate-to-vigorous physical activity**

Moderate to vigorous physical activity is shown to improve insulin sensitivity, body weight, CVD risk factors, adverse lipid levels, blood pressure, overall well-being, and reduces the risk of CV morbidity and mortality in patients with DM.

Recommendation

- Combination of aerobic and resistance exercise, for more than 150 min/week is recommended to reduce the future risk of developing CVD in patients with DM, unless contraindicated (e.g., severe comorbidities, limited life expectancy)

• Vitamin or micronutrient supplementation

Recommendation

- Vitamin or other food supplements is not recommended to reduce the risk of DM, or CVD in patients with DM.

11.4.2 Optimum glycemic control

Optimum glycemic control is proven to be effective in reducing micro-vascular complications. Long term follow-up of patients in UKPDS study and more recently cardiovascular outcome trials (COTs) in patients with DM have shown beneficial effects of glycemic control in reducing CVD related mortality or morbidity.

However, three major randomized controlled trials ACCORD, ADVANCE and VADT failed to show beneficial CV outcomes with intensive glycemic control ($\text{HbA1c} < 6.5\%$) compared to standard glycemic control. Compared to UKPDS study, these three studies included mostly patients with long standing DM (>10 years), or with other significant comorbidities (>10 years). Therefore, it is likely that intensive glycemic control is more beneficial in newly diagnosed or young patients with DM than the patients with long standing DM, other comorbidities or having established CVD.

Recommendation

- Young individuals with DM, or newly diagnosed DM patients with no other comorbidities
 - Tighter glucose control initiated leads to a reduction in CV outcomes over a 20-year timescale. However, tighter glucose control has no proven short term CV benefit.
- Patients with long standing DM (>10 years), elderly patients with DM, patients with DM and other significant comorbidities e.g., CVD, CKD, heart failure
 - As major studies have not shown benefit on CV outcomes with intensive glycemic control ($\text{HbA1c}<6.5\%$) compared to standard glycemic control, less-rigorous targets should be considered in these patients.
- Patients with DM with clinical CVD
 - Patients with T2DM with clinical CVD and with an eGFR $> 30\text{mL/min}/1.73\text{ m}^2$ in whom glycemic goals are not achieved with current oral hypoglycaemic agent(s) an oral hypoglycaemic agent with demonstrated CV outcome benefit should be added to reduce the risk of major CV events.

11.4.3 Optimum blood Pressure control

Hypertension is a major risk factor for both CVD and microvascular complications and many studies have shown that antihypertensive therapy reduces CVD events, heart failure, and microvascular complications in patients with DM.

Recommendation**• Blood pressure measurement**

- Blood pressure should be checked on every clinic visit, and patients found to have elevated blood pressure of $\geq 140/90$ mmHg should have confirmation of high blood pressure using multiple readings, including measurements on a separate day. (Grade C, consensus)

• Initiation of anti-hypertensive therapy

- Patients with confirmed office-based blood pressure $\geq 140/90$ mmHg should be initiated on lifestyle therapy (weight reduction, dietary modification by reducing salt intake and stress management).
- Patients with confirmed office-based blood pressure $\geq 140/90$ mmHg should be started on pharmacologic therapy and titrated appropriately to achieve appropriate blood pressure target (see below)

• Blood pressure targets

- SBP target of < 130 mmHg is appropriate if tolerated, but not < 120 mmHg. In older people (aged > 65 years), the SBP goal is to a range of 130 - 139 mmHg.
- DBP target of 70 - 80 mmHg is appropriate for most patients.

• Pharmacological agents

- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers).
- Multiple-drug therapy is generally required to achieve blood pressure targets.
- Combination of ACE inhibitors and angiotensin receptor blockers with direct renin inhibitors should not be used.
- An ACE inhibitor or angiotensin receptor blocker (at the maximum tolerated dose indicated) is the recommended first-line treatment for hypertension in patients
 - With diabetes and urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine.
 - With diabetes and urinary albumin-to-creatinine ratio 30–299 mg/g creatinine.
- For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually.

11.4.4 Antiplatelet therapy

Studies that examined the efficacy of aspirin as a primary CVD preventive strategy showed conflicting results with some studies showing modest benefit (Antithrombotic Trialists' Collaboration, ASCEND), while others (ARRIVE, ASPREE) showing no benefit of aspirin on the

occurrence of CV events. Overall, aspirin appears to have a modest effect on ischemic vascular events, with highest benefit seen in patients with higher cardiac risk. Most studies showed significantly increased risk of major bleeding especially gastrointestinal bleeding and other extracranial bleeding in patients treated with aspirin. Therefore, in patients with DM and no previous cardiovascular events, the overall benefit of aspirin is uncertain.

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention) and is strongly recommended.

Recommendation

As primary prevention

- Aspirin or clopidogrel should not be prescribed routinely to patients with DM.
- Aspirin is also not recommended for patients with DM at moderate CV risk as a primary preventive measure.
- Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in patients with DM at high/very high risk or WHO/ISH risk score >20% (see CVD risk table above), after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding.
- For patients over the age of 70 years, the risk of bleeding is greater than benefit. Thus, for primary prevention, aspirin is not generally recommended

As secondary prevention

- Aspirin (75 mg to 162 mg daily) is recommended for secondary prevention of CVD in those with DM and established CVD.
- Clopidogrel 75 mg may be used in people unable to tolerate aspirin.
- Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor such as clopidogrel) is reasonable for a year after an acute coronary syndrome.

11.4.5 Lipid-lowering agents

11.4.5.1 Statins

There is strong and consistent evidence of benefit of statins in preventing CV events and reducing CV mortality in patients with DM. Therefore, statins should be used for primary and secondary prevention of CVD/CAD deaths in patients with diabetes. It is estimated that reduction of LDL-C by 40 mg/dL with statins is associated with a 9% reduction in all-cause mortality and a 21% reduction in the incidence of major CV events in patients with DM.

Recommendation

Table 11. 2: Determining CVD events risk

	Patient characteristics	Statin types
Primary prevention (No established CVD)	All people with diabetes ≥40 years (40-75) of age Age 20–39 years with one or more CVD risk factors Age > 40 years with multiple other CVD risk factors For patients of all ages with 10- year CVD risk >20%	Moderate-intensity statin (Grade A) (e.g., Atorvastatin 40 -80 mg, rosuvastatin 20-40 mg, Simvastatin 20–40 mg) Moderate-intensity statin High-intensity statin therapy (e.g., Atorvastatin 40 -80 mg, rosuvastatin 20-40 mg) High-intensity statin therapy should be added to lifestyle therapy.
Secondary prevention with established CVD	Established CVD If LDL cholesterol is ≥70 mg/dL in a very high-risk patient (e.g: recent acute coronary syndrome) while on maximally tolerated statin dose Age >75 years already on statin therapy,	High-intensity statin therapy Add ezetimibe or PCSK9 inhibitor It is reasonable to continue statin treatment.

Two studies namely the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and ACCORD studies showed that use of fenofibrate on top of statins significantly reduced CV events in patients who have both elevated triglyceride and reduced HDL-C levels.

Recommendation

- Fibrates are recommended in patients with DM having persistent low HDL-C and high triglyceride levels despite lifestyle intervention and statins.
- Fibrates may be administered in patients with DM who are statin intolerant and have high triglyceride levels.

11.4.5.3 Others (ezetimibe, a PCSK9 inhibitor)

- In patients at very high risk, with persistent high LDL-C despite treatment with maximum tolerated statin dose in combination with ezetimibe, or inpatients with intolerance to statins, a PCSK9 inhibitor is recommended.

Chapter 12

Complications of diabetes mellitus

12.1 Diabetic Retinopathy

12.1.1. Introduction

- 12.1.1.1. Diabetic retinopathy (DR) is a micro vascular complication of diabetes mellitus. DR is a combined result of tissue ischemia, oxidative stress, and tissue inflammation. Not managing these pathologies can lead to rapid progression of DR into advanced stages which will result in a significant visual loss for the patient.
- 12.1.1.2. It is a leading cause of visual impairment in working-age adults. The screening process and primary prevention of diabetic retinopathy varies according to the type of diabetes and age of disease onset.
- 12.1.1.3. Diabetic retinopathy can occur at any age. Early detection of retinopathy depends on educating patients with diabetes as well as their families, friends, and health care providers about the importance of regular eye examinations. It is recommended that the examination is performed even though the patient is asymptomatic. Patients must be informed that despite having good vision and no ocular symptoms, they may still have significant disease that needs treatment.

Table 12. 1: Classification of Diabetic Retinopathy

Type of DR	Grade
Non-proliferative DR	Mild
	Moderate
	Severe
Proliferative DR	Early
	High risk
	Advanced
Diabetic Maculopathy	Non-centre involving
	Centre involving

12.1.2. Background/ Non-Proliferative Diabetic Retinopathy (NPDR)

- 12.1.2.1. While defects in neurosensory function have been demonstrated in patients with diabetes mellitus prior to the onset of vascular lesions, the most common early clinically visible manifestations of diabetic retinopathy would include micro-aneurysm formation. Further microvascular damage leads to retinal capillary non-perfusion, intra-retinal haemorrhages, venous abnormalities, and intra-retinal microvascular abnormalities. Occlusion of precapillary arterioles result in nerve fibre layer infarcts (cotton wool spots)
- 12.1.2.2. During this stage, increased vasopermeability can result in retinal thickening and exudates at the central macula which may lead to loss or distortion of vision.



Figure 12. 1: Non-proliferative Diabetic Retinopathy (NPDR)

Non-Proliferative Diabetic Retinopathy (NPDR)

12.1.3. Proliferative Diabetic Retinopathy (PDR)

- 12.1.3.1. The proliferative stage results from closure of arterioles and venules with secondary proliferation of new vessels on the disc, retina, iris and in the filtration angle. These new vessels can lead to bleeding, traction on the retina and neovascular glaucoma. Vision can be lost due to vitreous haemorrhages and tractional retinal detachments.



Figure 12. 2: Proliferative Diabetic Retinopathy



Figure 12.3: PDR with Vitreous Hemorrhage

12.1.4. Diabetic Maculopathy/ Diabetic Macular Oedema (DMO)

12.1.4.1. Capillary non perfusion and leakage in the macular region will result in diabetic maculopathy.

It will present with oedema, exudates, haemorrhages and micro-aneurysms in the macular region and can broadly be classified into a) non-centre involving, b) centre involving. Centre involving diabetic maculopathy can result in a significant reduction in visual acuity



Figure 12. 4: Diabetic Maculopathy

12.1.5. Care pathway for Diabetic Retinopathy

- 12.1.5.1. The clinician in charge of the patient should inquire about changes of vision, perform an **ophthalmic examination of the fundus** (or examine high quality retinal images) and adhere to a vigilant follow-up. An effective screening program can determine who requires an annual screening and who needs referral to an ophthalmologist for close follow-up and possible treatment
- 12.1.5.2. It is recommended that **HbA1c** of 7.0% or lower is kept as the target in most patients, while in selected patients with advanced retinopathy there is a benefit of setting a target of 6.5%. At the time of the eye examination, patients should be counselled about the importance of maintaining a near-normal blood glucose level, a normal blood pressure and monitoring serum glycosylated haemoglobin levels, which may lessen the risk of retinopathy developing and progressing.
- 12.1.5.3. It is recommended to continue **aspirin** in patients with proliferative diabetic retinopathy. There is no evidence to indicate an increased risk of vitreous haemorrhage.
- 12.1.5.4. It is recommended not to restrict normal **physical activity** in patients with any degree of diabetic retinopathy. However, it is recommended to restrict vigorous aerobic exercises and resistant training in patients with proliferative diabetic retinopathy due to the risk of vitreous haemorrhage. Physical activity does not appear to be associated with the regression or progression of retinopathy. For further information on exercise & diabetes mellitus refer chapter 16
- 12.1.5.5. It is recommended that a **referral** to an ophthalmologist be made when the patient has poor corrected vision (i.e.-wearing spectacles) or if there is any non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), or diabetic macular oedema (DMO).
- 12.1.5.6. Management of severe **NPDR and PDR** may involve laser photocoagulation treatment. Patients with vitreous haemorrhage and tractional retinal detachments may need retinal surgery.

12.1.5.7. Management of centre-involving **diabetic maculopathy** is by intra-vitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents and steroids. Laser photocoagulation remains the preferred treatment for non-centre-involving diabetic maculopathy. In patients with macular oedema, it is advisable to avoid pioglitazone.

12.1.6. Protocol for screening & referral for Diabetic Retinopathy

12.1.6.1. Screening is recommended to be done by,

- Consultant physicians and medical officers competent in describing basic details of direct ophthalmoscopic findings
- General practitioners competent in describing basic details of direct ophthalmoscopic findings
- Consultant eye surgeons and medical officers of eye clinics

12.1.6.2. It is recommended to perform the following steps for DR screening

- Patients' pupils should be dilated with mydriatic eye drops, G.Tropicamide 1% ± G.Phenylephrine 2.5%, instilled twice with a 15minute gap
- Patient should be examined 30 minutes following the instillation of first drop
- Direct ophthalmoscope or slit-lamp bio-microscope should be used to examine. Alternatively, high resolution 7-field digital fundus photography can be used

12.1.6.3. The first screening should be done as follows

- Children with Type 1 DM – 5ys after diagnosis or at 10year of age (whichever is earlier)
- Adults with Type 1 DM – At the time of diagnosis
- Children with Type 2 DM or other types – At the time of diagnosis
- Adults with Type 2 DM or other types – At the time of diagnosis
- In pregnancy (see section 12.1.6.5.)

12.1.6.4. The follow up & referral should be done as follows

12.1.6.4.1. No DR and having good, corrected vision (i.e., wearing spectacles)

- Annual follow up
- Can be done by the physician or medical officer competent in describing direct ophthalmoscopic findings

12.1.6.4.2. Other stages of DR or having poor corrected vision (i.e., wearing spectacles)

- To be referred to regional eye clinic or consultant eye surgeon
- Referral should be done within 1 month
- Follow up frequency and treatment will be determined by the consultant eye surgeon

12.1.6.4.3. Patients needing urgent referral (Need to admit and transfer)

- Sudden loss of vision in one or both eyes
- Noticing of sudden floaters or flashing lights (can indicate bleeding)
- Severe pain or headache following dilation of pupils (can indicate an angle-closure attack)
- Swollen optic discs (may indicate diabetic papillopathy)
- Severely disorganised retinal findings (large haemorrhages, fibrosis)

12.1.6.5. The recommended screening protocol in Pregnancy

12.1.6.5.1. Pre-existing DM

- First screening at the booking visit
- Then once every trimester
- If there is no DR, at least once during the postpartum year
- If DR is present, follow up by consultant eye surgeon

12.1.6.5.2. Gestational DM

- Definite diagnosis - screening not necessary
- Diagnosis not clear - Screen as pre-existing DM

The presence of DR, not a contraindication for vaginal delivery.

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12.2 Diabetic Neuropathy

12.2.1 Introduction

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. (Figure 12.5). The early recognition and appropriate management of neuropathy in patients with diabetes is important due to many reasons

1. Diabetic neuropathy is a diagnosis of exclusion. Non-diabetic neuropathies could be present in patients with diabetes and potentially treatable by specific measures.
2. A number of treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of diabetic peripheral neuropathies may be asymptomatic. If not recognized and preventive foot care is not implemented, patients are at risk for injuries to their insensate feet
4. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Classification of Diabetic Neuropathy

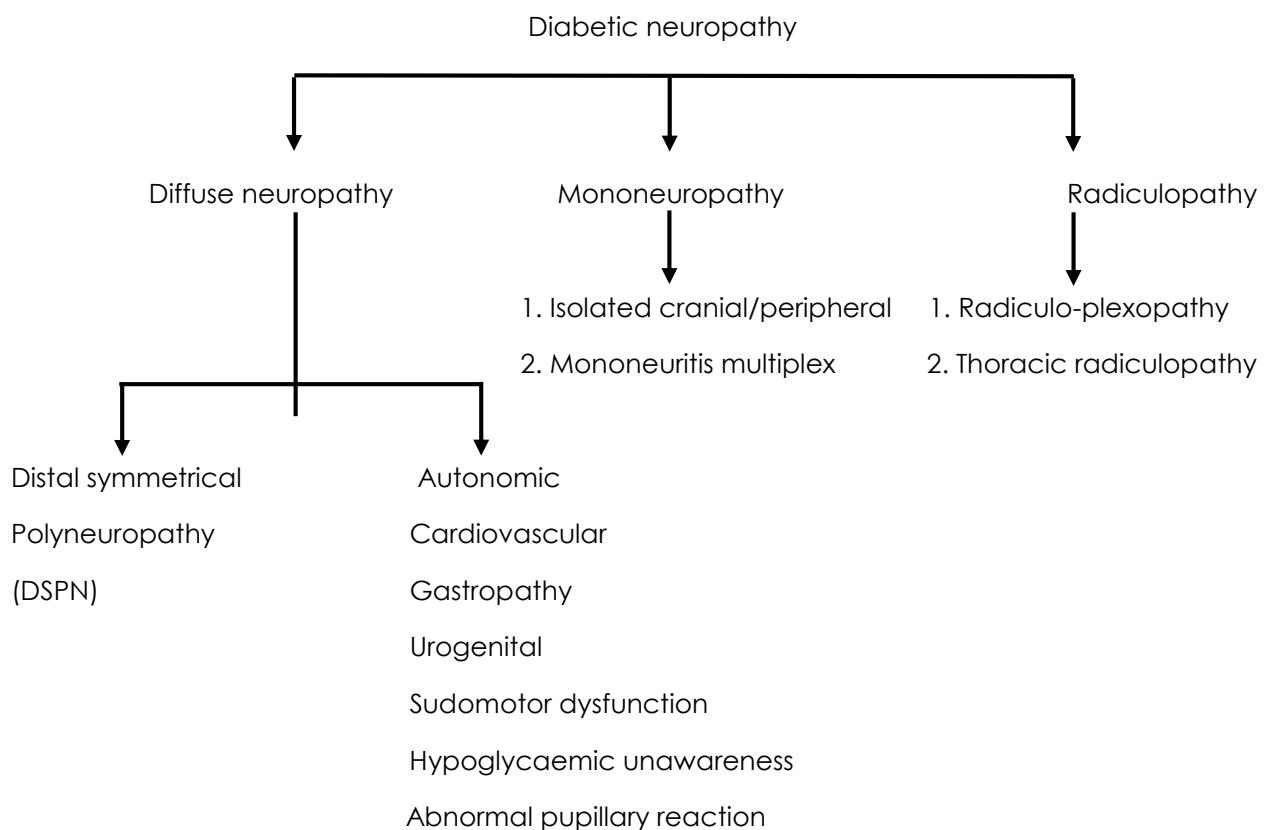


Figure 12. 5: Classification of Diabetic Neuropathy

12.2.2 Diffuse Symmetrical Polyneuropathy (DSPN)

Most common among diabetic neuropathies is chronic DSPN, accounting for about 75% of the diabetic neuropathies. A simple definition of DSPN for clinical practice is the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.

Definition of Distal Symmetrical polyneuropathy (DSPN)

Possible DSPN- Positive neuropathic sensation such as pain and dysesthesias due to small fiber involvement. (Burning, stabbing, or prickling pain) or negative sensation like paresthesia and numbness due to large fiber involvement mostly in the toes, feet, or legs. Symptoms characteristically worse at night. Signs of symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes.

Probable DSPN- Presence of any two or more of the following

- i) Neuropathic symptoms
- ii) Decreased Distal sensation
- iii) Decreased or absent Ankle reflexes

Confirmed DSPN-Defined by the presence of abnormal nerve conduction with symptoms and signs of Neuropathy.

It occurs in T1DM patients after many years of onset of DM. In T2DM, it can be associated even at the onset of disease and prevalence increases with the disease duration. There is emerging evidence that DSPN may be present in patients with prediabetes or metabolic syndrome.

Up to 50% of patients may experience symptoms of DSPN. Symptoms vary according to the class of sensory fibers involved.

12.2.3 Screening and Diagnosis of DSPN

Recommendations

1. It is recommended to assess for the DSPN at the onset of T2DM and 5 years after the onset in T1DM and then annually thereafter in both.
2. Consider screening patients with pre-diabetes who have symptoms of peripheral neuropathy.
3. Assessment should include a careful history and testing for either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (large-fiber function).
4. All patients should have an annual 10-g monofilament testing to assess their feet at risk for ulceration and amputation.

Indication for Referral to Neurologist

- Atypical Clinical feature
 - Motor>Sensory
 - Rapid Onset
 - Asymmetrical presentation
- Unclear diagnosis
- Possibility of differential aetiology

12.2.4. Management of DSPN

Recommendations

1. Tight glucose control targeting near-normal glycaemia is recommended for DSPN prevention in T1DM.
2. As glucose control has a more modest effect on the course of neuropathy in T2DM and metabolic syndrome, treatment should focus on normalizing lipids, blood pressure, weight, and glucose, along with lifestyle modifications to achieve a healthy diet and regular exercise.
3. It is recommended to offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain in DM (Table 12.2)
4. If the initial choice of drug is not effective/tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective/tolerated.
5. Consider capsaicin patch/ cream or lidocaine patches for people who wish to avoid, or who cannot tolerate, oral treatments or having localized neuropathic pain
6. If drug management has been successful consider reducing the dose and stopping therapy. A referral to a pain clinic is suggested for patients whose pain is unresponsive to conventional therapies.
7. In patients with severe and chronic pain tramadol or tapentadol may be used as the "last-line" therapy for a short duration prior referral to a pain clinic.
8. Electrical nerve stimulation or acupuncture may be an effective non-pharmacological option for painful neuropathy
9. Valproic acid or carbamazepine may be considered in reducing pain associated with neuropathy though it is not recommended as the first line.

Table 12. 2: Pharmacological agents used in DSPN

Class of the Drug	Name of the drug	Dose	Adverse Reactions
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Duloxetine	20 - 30 mg/ day maximum 60-120/ mg day	Nausea, somnolence, dizziness, decreased appetite, constipation, diaphoresis, and sexual dysfunction
	Venlafaxine	37.5mg/day, up to 75-225 mg/day	Adverse effects are like Duloxetine
Tricyclic antidepressants (TCAs) <ul style="list-style-type: none"> ▪ Amitriptyline ▪ Nortriptyline ▪ Desipramine 	Amitriptyline	10-25mg/day Maximum 100 mg/day	Dry mouth and somnolence. Urinary retention Contraindicated in patients with cardiac disease
Gabapentinoid anticonvulsants <ul style="list-style-type: none"> ▪ Pregabalin ▪ Gabapentin 	Pregabalin	75-150mg / day Maximum 300mg/day	Dizziness Somnolence Peripheral edema Weight gain.
	Gabapentin	100-300 mg/daily Maximum 900-3600 mg (single/divided doses-up to TDS)	somnolence, dizziness, and ataxia

12.2.5 Diabetic Autonomic Neuropathies

Autonomic neuropathies affect the autonomic neurons (parasympathetic, sympathetic, or both) and are associated with a variety of site-specific symptoms.

Table 12. 3: Symptoms and signs associated with Diabetic autonomic Neuropathy

Cardiovascular Autonomic Neuropathy (CAN)	Gastrointestinal Neuropathy	Urogenital Neuropathy	Sudomotor Neuropathy
Resting Tachycardia Abnormal Blood Pressure regulation -Non dipping -Reverse dipping Orthostatic Hypotension -light headedness -Giddiness -Visual impairment -Syncope Orthostatic tachycardia or bradycardia (Symptoms are similar with Orthostatic hypotension) Exercise Intolerance	Gastroparesis (Gastropathy) -nausea -Bloating -Loss of appetite -Early satiety -Postprandial vomiting -Brittle diabetes Esophageal dysfunction -Heartburn -Dysphagia for solids Diabetic diarrhea -profuse and watery diarrhea -fecal incontinence -may alternate with constipation Constipation -May alternate with explosive diarrhea	Bladder dysfunction -Frequency -Urgency -Nocturia -Hesitancy -Urinary incontinence/retention Male sexual dysfunction Female sexual dysfunction	Dry skin -Anhidrosis Gustatory sweating

12.2.5.1 Cardiovascular Autonomic Neuropathy (CAN)

CAN prevalence increases substantially with diabetes (Type 1 & 2) duration. It can be present in patients with impaired glucose tolerance, insulin resistance, or metabolic syndrome.

It is an independent risk factor for cardiovascular mortality, arrhythmia, silent ischemia, any major cardiovascular event, and myocardial dysfunction

12.2.5.1.1. Screening and Diagnosis

1. It is recommended to assess for the presence of autonomic neuropathy in patients with microvascular and neuropathic complications.
2. It is recommended to do investigations to rule out other co-morbidities or drug effects/interactions before considering the diagnosis of CAN.
3. In patients with hypoglycaemic unawareness, it is recommended to assess for the presence of cardiovascular autonomic neuropathy.

4. Optimize glucose control as early as possible to prevent or delay the development of CAN in people with T1DM.
5. Consider a multifactorial approach targeting glycemia among other risk factors to prevent CAN in people with T2DM.
6. Consider lifestyle modifications to improve CAN in patients with pre-diabetes.

12.2.5.1.2. Treatment of Orthostatic Hypotension.

1. Treatment for orthostatic hypotension involves both pharmacological and non-pharmacological interventions.
2. Physical activity and exercise should be encouraged and volume repletion with fluids and salt is mainstay in the management.
3. Low-dose fludrocortisone may be beneficial though there is a risk of supine hypertension.
4. When there is an element of neurogenic orthostatic hypotension, the administration of sympathomimetic medications is considered

E.g., Midodrine

12.2.5.2. Gastrointestinal Neuropathies

1. When a patient presents with gastroparesis, exclusion of organic causes of gastric outlet obstruction or peptic ulcer disease (with upper GI endoscopy or a barium study) is needed prior to investigating gastroparesis.
2. Dietary changes such as having frequent/multiple small meals and decreasing dietary fat and fiber intake may be helpful.
3. Withdrawing drugs with effects on gastrointestinal motility, such as opioids, anticholinergics, tricyclic antidepressants, GLP-1 agonists, DPP- 4 inhibitors, may improve intestinal motility
Metoclopramide, Domperidone and erythromycin are effective for short-term use

12.2.5.3 Urogenital Neuropathies

Diabetic autonomic neuropathy may cause genitourinary disturbances such as sexual dysfunction and bladder dysfunction.

In men, diabetic autonomic neuropathy may cause erectile dysfunction (ED) and/or retrograde ejaculation.

Diagnosis and Management

1. Consider screening men with other forms of diabetic neuropathy annually for ED.
2. ED may be a consequence of autonomic neuropathy. The other risk factors such as hypertension, hyperlipidemia, obesity, endothelial dysfunction, smoking, CVD, concomitant medication, and psychogenic factors have also to be looked for in men with ED.
3. Optimal glucose control is recommended to lower incidence of ED in men with T1DM, but evidence is less strong for T2DM.
4. Phosphodiesterase type 5 inhibitors are recommended as first-line therapy. Transurethral prostaglandins, intracavernosal injections, vacuum devices, and penile prosthesis are considered in more advanced cases.
5. Females with recurrent urinary tract infections (UTI) should be screened for urogenital autonomic neuropathy.
6. Bladder functions should be performed in patients with diabetes who have recurrent UTI or palpable bladder.

12.2.5.4 Sudomotor Dysfunction

- Sudomotor dysfunction may manifest as dry skin, anhidrosis, or heat intolerance
- A rare form of sudomotor dysfunction is gustatory sweating that comprises excessive sweating limited exclusively to the head and neck region triggered by food consumption or the smell of food. Gustatory sweating is also described in patients with diabetic nephropathy on dialysis.
- Topical antimuscarinic agent can be used in the treatment of gustatory sweating

12.2.6 Mononeuropathies and atypical neuropathy

- Mononeuropathies are due to vasculitis and subsequent ischemia or infarction of nerves. It commonly involves cranial nerves III, IV, VI, and VII and thoracic and peripheral nerves, including peroneal, sural, sciatic, femoral, ulnar, and median. It usually affects a single nerve, but multiple nerves can be affected.
- Their onset is acute, associated with pain, and their course is self-limiting, resolving over a period of 6 weeks.
- The entrapment neuropathies are highly prevalent in the diabetic patients, it should be actively sought in patients with the signs and symptoms of neuropathy because the treatment may be surgical.
- Common entrapments involve the median, ulnar, and peroneal nerves, the lateral cutaneous of the thigh, and the tibial nerve in the tarsal canal.

12.2.7 Diabetic Radiculoplexus Neuropathy

- Diabetic radiculoplexus neuropathy (diabetic amyotrophy or diabetic polyradiculoneuropathy) involves the lumbosacral plexus. It occurs mostly in men with T2DM. Extreme unilateral thigh pain and weight loss, followed by motor weakness are the main symptoms. Electrophysiological assessment is required to document the extent of disease and alternative etiologies, such as degenerative disc disease or neoplastic, infectious and inflammatory spinal disease.
- It is usually self-limiting, and patients improve over time with medical management and physical therapy.

12.2.8 Treatment-Induced Neuropathy in Diabetes (Insulin Neuritis)

- It is a rare iatrogenic small-fiber neuropathy caused by an abrupt improvement in glycemic control in the setting of chronic hyperglycemia, especially in patients with very poor glucose control. The management focuses on controlling the symptoms while they gradually improve with time.

12.3 Diabetic nephropathy

- Refer to section 15.4. Diabetes and Kidney

Chapter 13

Diabetic foot

13.1. Diabetic foot care service in Sri Lanka

Diabetic foot disorder (DFD) is one of the main long-term complications of diabetes. Main three pathologies of this disorder are neuropathy, deformity and peripheral arterial disease. DFD is associated with foot ulceration, lower limb amputations, premature deaths, poor socio-economic status and incurs significant financial burden on the patient, family and the healthcare system. Strategies to minimize these adversities are to provide multidisciplinary team care and close long term follow up along with establishing a community podiatry service.

Properly integrated three main services have been identified for the care of persons with DFD in Sri Lanka.

- **Community-based foot care service:** A community-based podiatry service is vital for this purpose preventing and early detection of DFD.
- **Hospital-based foot care service:** Since DFD is a surgically managed complication of a long-standing medical disease, both medical and surgical services should work synergistically to treat this condition. Hence clearly defined care pathways and protocols are necessary to deliver a coordinated service at all levels of hospitals in the government sector as well as in the private sector.
- **Orthotic service for diabetic foot care** - Availability of appropriate footwear and an orthotic service is an integral part of prevention and treatment of DFD.

13.1.1 Community based foot care service for a person with DFD

It is recommended

1. Primary physician / general practitioner responsible for the care of a patient with diabetes should ensure that the patient has undergone an annual interval foot assessment and receives structured foot care education.
2. Education should be carried out by a trained medical officer, nursing officer or podiatrist.
3. The patient's caregiver should also be involved with such educational sessions.
4. If the patient requires custom made therapeutic footwear, he/she should be referred to the closest orthotic service available.
5. If a patient presents with an acute foot problem (BOX 13.1), he/she should be referred to the nearby surgical or medical services as early as possible (preferably within 24 hours).
6. The responsible community care team should also be involved to ensure that the follow-up plan for the patient following discharge from acute services, is carried out as requested.
7. Specialized units should establish outpatient high risk foot clinics to provide focused and specialized care for persons with high-risk diabetic foot.

13.1.2 Hospital based foot care service for a patient with DFD

1. If a patient has a limb threatening or life-threatening DFD, they should be immediately referred to acute surgical services.

BOX 13.1

Limb-threatening and/or life-threatening DFD include the following:

- **Ulceration with fever and any other signs of sepsis**
- **Ulceration with limb ischemia**
- **Clinical concern that there is a deep-seated soft tissue or bone infection (with or without ulceration)**
- **Gangrene (with or without ulceration)**

2. For all other active DFD, refer the patient immediately to an outpatient surgical clinic. These patients should not be waitlisted and should be seen on the next available clinic date.
3. All the patients with DFD should be jointly managed by surgical and medical services.
4. Acute foot problems should be attended to within 24 hours of referral.
5. The consultant under whom the patient is admitted, should be accountable for the overall care of the patient. He/she should ensure coordinated and integrated care in a timely manner for the DFD with inputs from relevant specialties.
6. If a required service is not available for the DFD in the local hospital, escalation to a hospital that offers that particular service, should be carried out without a delay.
7. If provisions are available to establish a multidisciplinary foot care service within the hospital, the following specialties should be included.
 1. Physician / Endocrinologist
 2. General Surgeon, Vascular surgeon, Orthopedic surgeon, Plastic surgeon
 3. Radiologist/ Interventional radiologist
 4. Microbiologist
 5. Nursing officer, Diabetic Education Nursing Officer (DENO)
 6. Podiatrist
 7. Orthotist
 8. Nutritionist
 9. Psychologist
 10. Physiotherapist and Occupational therapist
 11. Social service officer
8. Each hospital should have a defined care pathway and standard operating procedures for management of patients with DFD to provide efficient service to the patients.

13.1.3 Orthotic service for a patient with DFD

1. A patient with high-risk feet (see table 13.1) and with foot ulcers are recommended to be evaluated by an orthotist to perform the necessary modifications of existing footwear or for prescription of therapeutic footwear.
Therapeutic footwear should be reviewed regularly by orthotist to ensure adequate fit and to perform necessary alterations as demanded by changing clinical circumstances.
2. Orthotists should coordinate with the treating physician regularly to provide optimum care for the patient with DFD and to avoid complications that could arise due to an ill-fitting prescribed footwear (IC).

13.2. Risk stratification and management of a person with DFD

It is recommended

- 13.2.1. To assess the person's current risk of developing a DFD using the following risk stratification (see Table 13.1)
- 13.2.2. Depending on the patient's risk of developing a diabetic foot problem, carry out reassessments at the following intervals.

Table 13. 1: Risk stratification of developing diabetic foot problems

Risk level	Low risk	Moderate risk	High risk	Active diabetic foot problem
Features	No risk factors present except callus alone.	Any of: -deformity or -neuropathy or -non-critical limb ischemia (CLI).	Any of: - previous ulcer - previous amputation - neuropathy with non-CLI - neuropathy with callus and/or deformity - non-CLI with callus and/or deformity - On renal replacement therapy	Any of: - Ulcer - Spreading infections - Critical limb ischemia - Gangrene or - suspicion of an acute Charcot arthropathy - Unexplained hot, red, swollen foot
Action	Assess annually	Assess every 3-6 months	Assess every 1-3 months	Urgent referral

13.2.3 The patient should be assessed very frequently (e.g., every 1–2 weeks) for people who are at high risk, if there is immediate concern of developing an active diabetic foot problem.

13.2.4 Refer to acute medical or surgical service if there are any active foot problem

13.2.5 Examination

13.2.5.1 Examination should include testing for peripheral neuropathy using Semmes-Weinstein test or Ipswich touch test

13.2.5.2 Examine the feet for deformities. Commonly seen deformities in a person with diabetes are claw toe, hammer toe, bunion, overlapping digits and chronic Charcot foot deformity.

13.2.5.3 Assessment for peripheral arterial disease (PAD) in all patients (See section 13.4).

13.2.6 Management

13.2.6.1 To reduce risk of DFD and lower limb amputation it is suggested to maintain HbA1c of less than 7%.

13.2.6.2. Regular shaving of callus, debulking and trimming of nails by a trained health care professional.

13.2.6.3 Prophylactic arterial revascularization for persons with PAD to prevent future diabetic foot ulcerations is not recommended.

13.2.6.4 Education should be done at an early stage of diabetes and should be repeated periodically. A regular structured education program (both verbal and written) should highlight the following components.

- Basic foot care advice - daily inspection, cleaning and moisturization of feet, transverse nail trimming
- Importance of foot care.
- The person's current individual risk of developing a foot problem.
- Footwear advice and recommendations of suitable footwear.
- Foot emergencies (Table 13.1) and points of contact.
- The importance of blood glucose control in preventing DFD and complications

13.2.7. Footwear

13.2.7.1 Routine use of specialized therapeutic footwear in patients with low-risk feet is not recommended.

13.2.7.2 Customized therapeutic footwear should be used for people with high-risk feet (including those with previous history of ulcers, partial amputations of the foot or chronic Charcot foot) or people with significant deformity that leads to formation of recurrent callus.

13.3 Management of a person with a Diabetic foot ulcer

It is recommended,

13.3.1 One or more of the following should be used as standard care for treating diabetic foot ulcers:

- Wound debridement
- Antibiotics
- Wound dressings.
- Treat ischemia.
- Off-loading.

13.3.2 Evaluation for diabetic foot infection (DFI) and surgical debridement should be done urgently by an experienced medical practitioner to treat abscesses, necrotizing fasciitis and suppurative necrosis.

13.3.3 Initial sharp debridement followed by usage of other debridement methods can be used based on the clinical context.

13.3.4 Early vascular surgical opinion should be sought if the peripheral pulses are not palpable to prevent amputation due to ascending sepsis and gangrene.

13.3.5 Aseptically collected tissue specimen over a swab is recommended to perform culture and antibiotic sensitivity tests in soft tissue infection.

13.3.6 The most current local guideline according to local sensitivity patterns should be followed when selecting empirical antibiotics to treat DFI.

13.3.7 Diabetic foot osteomyelitis (DFO)

If suspected serial X-rays (**See Box 13.2**) and probe to bone (PTB) test can be used confirm the diagnosis radiologically and clinically. MRI is the study of choice in case of a diagnostic difficulty. Aseptically performed bone biopsy for culture and sensitivity testing and/or histology can confirm DFO. DFO requires a minimum of 6 weeks to 3 months course of antibiotics based on the sensitivity pattern to eradicate osteomyelitis medically. Failed medical therapy can be an indication for surgical treatment for DFO.

Box 13.2

Features of diabetic foot osteomyelitis on plain X-ray

- Loss of bone cortex with bony erosions
- Focal loss of trabecular pattern or marrow radiolucency
- Periosteal reaction
- Bone sclerosis
- Soft tissue density /gas
- Sequestrum/Involucrum/ cloacae (less seen in DFO)

13.3.8 Dressings - cost effective and simple dressing products that enable to achieve desired moisture balance in the management of diabetic wounds should be used.

13.3.9 Frequent evaluation of wound to assess progression of wound healing and performing sharp debridement of necrotic tissue and surrounding callus regularly should be performed as indicated during the follow up visits.

13.3.10 Wounds that are not reduced in size (area) by 50% within 4 weeks of standard wound care and offloading will be considered as having undesirable wound healing trajectory.

13.3.11 If the wounds fail to improve, re-evaluate vascular status and offloading strategy before considering adjuvant wound therapy methods, such as negative pressure dressing, biological agents, and other adjuvant therapies.

13.3.12 Offloading the Ulcer

- Offer non-removable total contact casting (TCC) to offload plantar neuropathic, non-ischemic, uninfected forefoot and midfoot diabetic ulcers.
- Offer an alternative offloading device until casting can be provided. In persons with non-plantar ulcers, offloading can be done using locally available modality that relieves undue pressure over the wound.
- Surgical offloading strategies (tenotomies, tendon lengthening, tendon transfers, osteotomies, and arthrodesis) should be reserved for resistant ulcers and frequently recurring ulcers in spite of the usage of appropriate offloading footwear and it should be performed by a trained specialist in such procedures.
- Prophylactic reconstructive surgeries to improve biomechanics of the patient with DFD may need a multidisciplinary approach.

13.4. Assessment and management of a patient with a diabetes and peripheral arterial disease (PAD)

It is recommended

Table 13. 2: Interpretation of Ankle Brachial Pressure Index (ABPI)

ABPI*	Interpretation
>1.3	Incompressible vessels
0.9-1.3	No significant PAD
0.8-0.9	Mild PAD
0.5-0.8	Moderate PAD
<0.5	Severe PAD
<0.3	Critical PAD

*Interpretation of ABPI in diabetes should be done with caution due to the calcification of the arterial wall

13.4.1 Clinical assessment of peripheral vascular system includes eliciting peripheral stigma of PVD, palpation of lower limb peripheral pulses including dorsalis pedis and posterior tibial pulses and measurement of ankle brachial pressure index (ABPI). This measurement should be done in all persons with diabetes who are:

- Older than 50 years of age
- Having diabetes for more than 10 years
- Having other cardiovascular comorbidities
- With a past history of diabetic foot ulcer or amputation.
- With an active foot ulcer.
- With a past history of lower limb revascularization

13.4.2 If the facilities are available, toe brachial pressure index and doppler arterial waveforms and velocities of the pedal and ankle arteries can be assessed by using handheld doppler and photo plethysmography.

13.4.3 Patients with DFU who have PAD should be referred to a vascular surgeon without delay.

13.4.4 Revascularization is recommended using either bypass surgery or endovascular therapy.

13.4.5 Any center offering revascularization for DFU should have rapid access to diagnostic tests (duplex studies and Angiography) and therapeutic intervention (operating theatre, angiointerventional facility) to minimize tissue loss due to progressive ischemic necrosis and to prevent amputations due to undue delay.

13.4.6 Medical therapy for the patients with PAD,

- Recommending antiplatelet therapy for an asymptomatic patient with PAD (ABPI<0.9) may reduce risk of MACE.
- Single antiplatelet therapy using Aspirin or clopidogrel is recommended for patients with symptomatic PAD.
- Effectiveness of dual antiplatelet therapy (DAPT) as a cardiovascular risk reduction in patients with PAD is not well established.
- Ticagrelor in comparison with clopidogrel is not recommended for patients with symptomatic PAD.
- DAPT may reduce risk of major adverse limb events (MALE) after lower limb revascularization.
- The use of low dose Aspirin and rivaroxaban (2.5mg BID) may reduce risk of MACE and MALE.
- High dose statins are recommended for patients with PAD.
- Anti-hypertensive medications are recommended for patients with PAD and hypertension.
- Use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers can be effective to reduce MACE in patients with PAD.
- Abstinence from cigarette smoking and other forms of tobacco usage should be advised at every visit.
- Cilastazole is an effective therapy in the treatment of intermittent claudication.
- There is no significant benefit in cilastazole in CLI.
- Pentoxifylline is not effective for treatment of PAD.

13.5. Charcot arthropathy

It is recommended

13.5.1 Acute Charcot Arthropathy (ACA) poses a real clinical challenge as it mimics many other common conditions like cellulitis, venous edema, lymphoedema etc. Failure to diagnose this condition at the beginning, could progress into irreversible gross deformity of the foot (Chronic Charcot disease (CCD)), which leads to recurrent ulceration osteomyelitis and amputation.

13.5.2 Suspect ACA if there is redness, warmth, swelling with or without deformity/pain (in particular, when the skin is intact), especially in the presence of peripheral neuropathy or renal failure.

13.5.3 Once the ACA is suspected, consider immediate immobilization using a non-removable offloading device (Total Contact Cast -TCC) or irremovable walker (IW) with offloading insole. Removable walkers with offloading insoles should be offered to a person only if TCC and IW are deemed inappropriate.

13.5.4 If ACD is suspected, perform weight-bearing X-ray of the affected foot and ankle (See figure 13.1). Consider an MRI if the X-ray is normal but Charcot arthropathy is still suspected. Contrary to an infection in acute Charcot arthropathy all the inflammatory markers like Full Blood Count, C reactive protein level and Procalcitonin level may be normal.

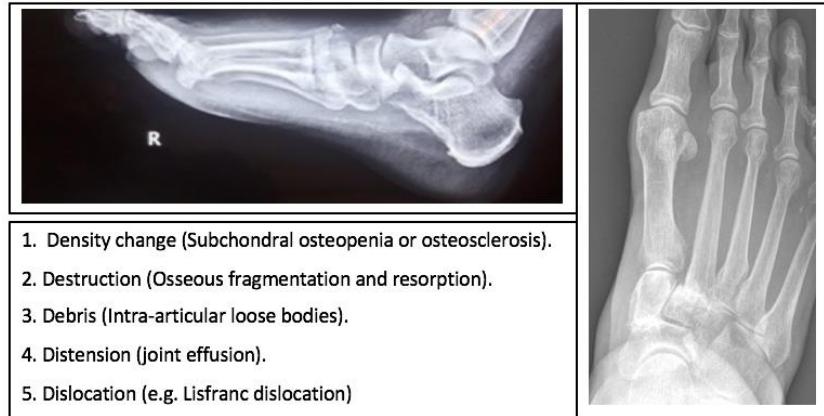


Figure 13.1: Plain X-ray features of early Charcot arthropathy (Five "D"s).

- 13.5.5 Usage of bisphosphonates to treat ACA is not recommended.
- 13.5.6 Once the diagnosis is confirmed, immobilization, adequate education, emotional support should be provided, and patient reviewed every 1-2 weekly for symptoms improvement and TCC/ IW fit. Treatment duration can be varied between 2 – 12 months.
- 13.5.7 Monitor the treatment of ACA using clinical assessment, measuring foot–skin temperature difference and taking serial X-rays.
- 13.5.8 Acute Charcot arthropathy is likely to resolve when there is normalization of clinical features, presence of sustained temperature difference of less than 2 degrees between feet and
X-ray changes show remodeling phase. If the foot remains unstable and not showing any evidence of healing the patient should be referred to an orthopedic surgeon.
- 13.5.9 Patients who have a chronic foot deformity as a result of previous acute Charcot arthropathy are at a high risk of ulceration and should be cared closely by the orthotist, surgical (Orthopedic) and medical teams.

Chapter 14

Management of Diabetic Emergencies

Diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state (HHS) are the two most serious acute hyperglycemic metabolic complications of diabetes.

14.1. The Management of Diabetic Ketoacidosis in Adults

The triad of uncontrolled hyperglycemia, metabolic acidosis, and ketonaemia characterizes DKA.

14.1.1 Diagnostic Criteria

- ❖ All three of the following must be present

Box 14.1

- ❖ Ketonaemia $> 3.0 \text{ mmol/L}$ or significant ketonuria (more than 2+ on standard urine sticks)
- ❖ Blood glucose $> 200 \text{ mg/dL}$ (11.0 mmol/L) or known diabetes mellitus
- ❖ Bicarbonate (HCO_3^-) $< 15.0 \text{ mmol/L}$ and/or venous pH < 7.3

- Can use ketonuria ++ or more if blood ketone level is not available. (ONLY for diagnostic purposes, not management)

Euglycemic DKA,

1. Occurs in which the serum glucose is normal or near normal, particularly in patients with poor oral intake, treatment with insulin prior to arrival in the emergency department, in pregnant women, and in patients on sodium-glucose co-transporter 2 (SGLT2) inhibitors.
2. When SGLT2 inhibitors block the sodium-glucose co-transporter 2, the resulting glucosuria can minimize or prevent the development of hyperglycemia, despite very low insulin levels/activity and development of ketoacidosis.
3. In these individuals, the absence of substantial hyperglycemia delays recognition of the DKA by clinicians.
4. Need to start 10% glucose at the beginning to prevent hypoglycaemia in these patients.

14.1.2. Pathogenesis

- Metabolic derangements result from the combination of absolute or relative insulin deficiency and an increase in counter regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone).
- Most patients with DKA have T1DM, however, patients with T2DM are also at risk during the catabolic stress of acute illness such as trauma, acute coronary syndrome, surgery, or infection.

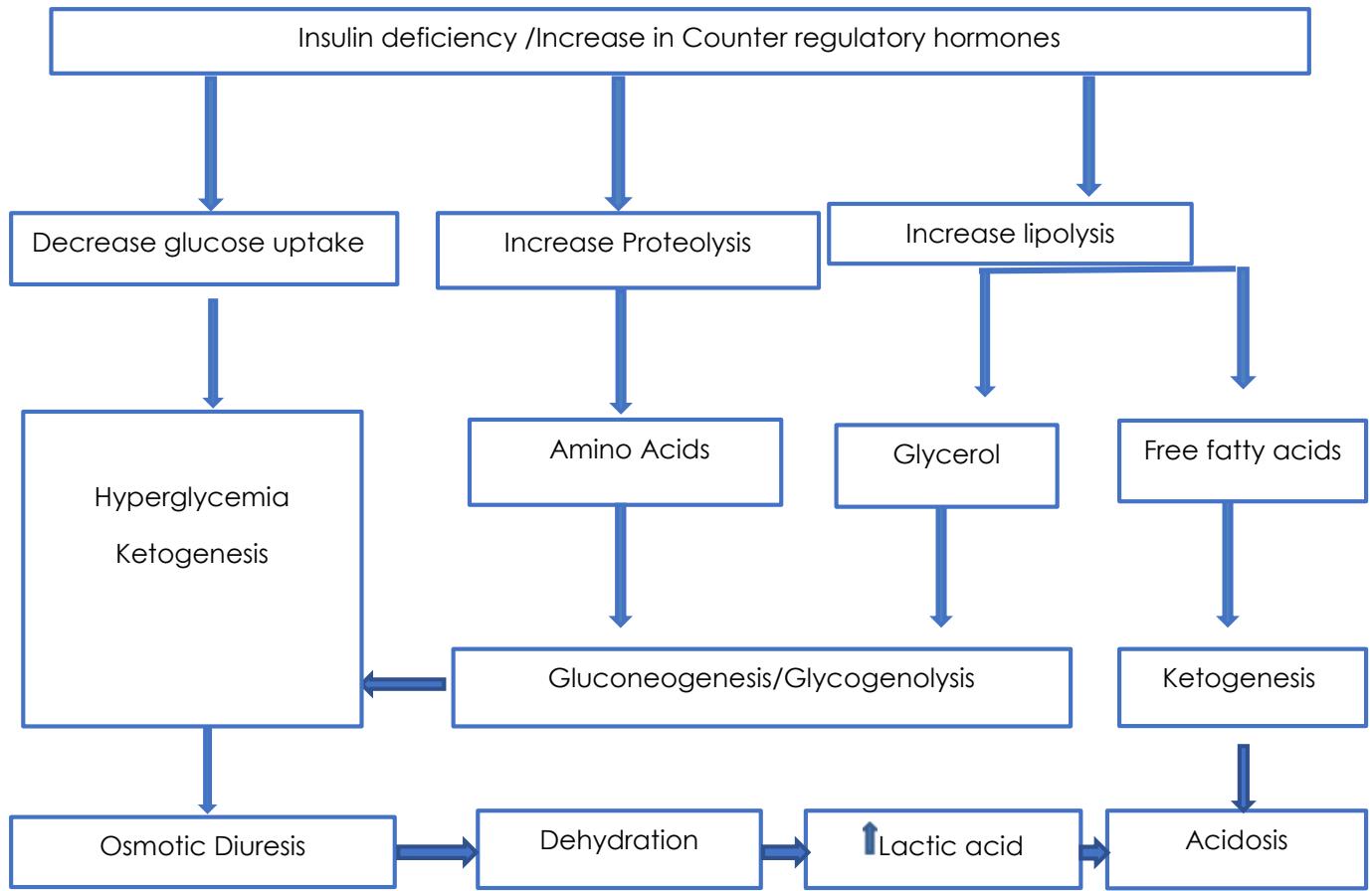


Figure 14. 1 Pathophysiology of Diabetic ketoacidosis

14.1.3. Management

Management principles

- Optimization of
 - 1) Volume status
 - 2) Hyperglycemia and ketoacidosis
 - 3) Electrolyte abnormalities
 - 4) Potential precipitating factors
- The main aims giving fluids are:
 - Restoration of circulatory volume
 - Clearance of ketones
 - Correction of electrolyte imbalance

14.1.3.1. Stage 1. Immediate Management on Diagnosis (0 to 60 minutes)

Patient Assessment Box 14.2

- Rapid ABC
- Large bore IV cannula and take blood for following investigations
- Start IV fluid as below
- Rapid clinical assessment : Respiratory rate, pulse rate, temperature and blood pressure
- Oxygen saturation and Glasgow Coma Scale
- (If GCS low –NG tube insertion and may need input from critical care team
- Complete clinical examination should follow

Initial investigations should include Box 14.3:

Bedside test: capillary blood glucose, blood ketone bodies, VBG

- | | |
|--|---|
| <ul style="list-style-type: none">• Blood ketone• Capillary blood glucose• Venous plasma glucose• Venous blood gas• Full blood count• Pregnancy test in females if clinically indicated | <ul style="list-style-type: none">• Urea and electrolytes• Blood cultures• ECG• Chest radiography if clinically indicated• Urinalysis and culture |
|--|---|

- ❖ VBG is recommended over ABG. Do ABG ONLY if the patient has a reduced conscious level or hypoxemia.

Table 14. 1: Initial fluid resuscitation, Insulin administration and potassium correction

Complete initial evaluation, confirm diagnosis			
1. Initial fluid resuscitation	2. Start insulin	3. Potassium correction	
Fluids	Insulin	Potassium	
IV. 0.9% Saline as the fluid of choice to resuscitate the patient. Once BG < 14mmol/l (<250mg/dL) commence 10% glucose at 125mls/hr ALONG SIDE THE 0.9% Saline. (Need to adjust rate of 0.9% saline infusion if clinically indicated)	Start Insulin infusion at a fixed rate of 0.1 unit/kg/hr (Maximal initial dose of insulin is 15 units) Continue FRII throughout and Do not reduce insulin dose until resolution of DKA	Serum level	Replacement
		>5.5	Nil
		3.5-5.5	40 mmol/ L of NS
		<3.5	40 mmol/L of NS. Senior review as additional potassium required
		♦ If initial potassium is <3.5 mmol/L- replace potassium till 3.5 mmol/L before starting insulin	

14.1.3.1.1. Initial fluid Replacement

It is recommended to start intravenous 0.9% saline as below as it is the first and the most important step of the management of DKA.

14.1.3.1.1.1. SBP on admission <90 mmHg

- Give 500ml of 0.9% sodium chloride solution over 10-15 minutes.
- If SBP remains below 90mmHg, need to give another 500 ml of 0.9% saline.
- In practice most patients will require between 500 to 1000ml given rapidly
- If there has been no improvement reconsider other causes of hypotension (Cardiogenic shock, Sepsis etc)
- Once SBP >90mmHg, give 1000ml 0.9%NaCl over the next 60minutes.
- Addition of potassium likely to be required in this second litre of fluid if indicated depending on serum potassium level

14.1.3.1.1.2. If SBP >90 mmHg

- IV normal saline 1000 ml for first hour

14.1.3.1.1.3. Crystalloid Vs colloid

- There is a potential risk of increased morbidity and mortality associated with use of colloid. Hence, use of crystalloid is recommended, and colloid should be avoided.

14.1.3.1.2. Intravenous insulin

Start Insulin infusion

- At a fixed rate of 0.1 unit/kg/hr (If weight is not available from the patient, estimate it in kilograms and if the patient is pregnant, use her present weight)
 - A priming dose of insulin is not recommended.
 - A bolus (stat) dose of intramuscular insulin (0.1 unit/kg) is suggested only if there is a delay in setting up a FRII.
 - Continue FRII throughout and **DO NOT reduce insulin dose until resolution of DKA.**
 - If the glucometer reads “blood glucose as “Hi”, venous blood should be sent to the laboratory hourly or measured using VBG until the bedside meter gives the exact value.
- ❖ If the patient is already on long-acting insulin, it is recommended to continue the usual dose of long-acting insulin to prevent rebound hyperglycemia once IV insulin is stopped.

Calculation of the insulin dose for weight

Table 14. 2: Calculation of the insulin dose for weight

Weight Kilogram	in	Insulin dose per hour (units)	Weight Kilogram	in	Insulin dose per hour (units)
30-39		3	100-109		10
40-49		4	110-119		11
50-59		5	120-129		12
60-69		6	130-139		13
70-79		7	140-149		14
80-89		8	>150		15
90-99		9			

14.1.3.1.3. Potassium replacement

- Hypokalaemia and hyperkalaemia are life threatening conditions and common in patients with DKA.
- Serum potassium is often high on admission (although total body potassium is low)
 - ❖ If initial potassium is <3.5 mmol/L replace potassium up to 3.5 mmol/L before starting insulin
 - ❖ Life threatening hypokalemia can occur with insulin infusion due to precipitous falls upon treatment with intravenous insulin
 - **Regular (2 hourly) monitoring of potassium is mandatory**
 - **Cardiac monitoring is mandatory If K⁺ infusion is greater than 20mmol/hour**
 - Potassium replacement must be done cautiously if renal function remains impaired and/or urine output does not increase at least to 0.5ml/kg/hour.

Box 14.3

Indication of severe DKA and may require admission to HDU and insertion of CV line needed

The presence of one or more of the following may indicate severe DKA.

- **Blood ketones over 6mmol/L**
- **Bicarbonate level below 5mmol/L**
- **Venous/arterial pH below 7.0**
- **Hypokalaemia on admission (under 3.5mmol/L)**
- **GCS less than 12 or abnormal AVPU scale**
- **Oxygen saturation below 92% on air (assuming normal baseline respiratory function)**
- **Systolic BP below 90mmHg**
- **Pulse over 100 or below 60bpm**
- **Anion gap above 16**

14.1.3.1.4. Identify and treat precipitating cause appropriately.

14.1.3.1.5. Place of Bicarbonate administration

- Adequate fluid and insulin therapy will resolve the acidosis in DKA
- In most cases bicarbonate is NOT helpful and is potentially dangerous and slows the rate of recovery of ketosis.
- Bicarbonate should **ONLY** be considered if pH is persistently <6.9 despite adequate resuscitation and need to decide on individual basis.
- If bicarbonate is being considered, the patient should be in a level 2 (HDU / ICU) environment
- Only consider after discussion with the consultant in charge of the patient's care

14.1.3.1.6. Place of thromboprophylaxis

- Consider **thromboprophylaxis** with low-molecular weight heparin in older patients or high-risk patients, unless it is contraindicated

14.1.3.2. Stage 2: 60 minutes to 6 hours

Aims:

- Achieve metabolic targets
- Maintain serum potassium in the normal range
- Avoid hypoglycaemia
- Continue treating precipitating factors appropriately

Box 14.4

Metabolic targets

- Reduction of the blood ketone concentration by 0.5mmol/L/hour
- Increase the venous bicarbonate by 3.0mmol/L/hour
- Reduce capillary blood glucose by 3.0mmol/L/hour
- Maintain potassium between 4.0 and 5.5mmol/L

Box 14.5

Action 1 – Re-assess patient, monitor vital signs

- Patients should be re-assessed hourly initially to ensure metabolic targets are being achieved.
- If the patient is anuric by 60 minutes, need urinary catheterization.
- Maintain an accurate fluid balance chart, the minimum urine output should 0.5ml/kg/hr
- Consider naso-gastric tube insertion if the patient is obtunded or persistently vomiting
- If the oxygen saturation falls, need an arterial blood gas measurement and a repeat chest radiograph
- Regular observations and Early Warning Score (EWS) charting as appropriate
- Continuous cardiac monitoring in those with severe DKA

Monitoring

- Hourly capillary glucose and ketone measurement
- Venous pH, HCO₃ -, potassium at 60 minutes, 2 hour and 2 hourly after that
- 4 hourly laboratory electrolytes

Action 2: IV Fluid

Below is a table outlining a typical fluid replacement regimen for a previously well 70kg adult from 2nd hr. This is an illustrative guide only.

Table 14. 3: IV Fluid replacement regimen

Fluid	Volume
0.9% sodium chloride 1L + KCl	1000ml over next 2 hours
0.9% sodium chloride 1L + KCl	1000ml over next 2 hours
0.9% sodium chloride 1L + KCl	1000ml over next 4 hours
0.9% sodium chloride 1L + KCl	1000ml over next 4 hours
0.9% sodium chloride 1L +KCl	1000ml over next 6 hours

If 0.9% sodium chloride with pre-mixed KCl is not available, IV KCL can be added to 0.9% sodium chloride depending on replacement requirement

Slower infusion rate should be considered

- Young people aged 18-25 years
- Elderly
- Pregnant
- Heart or renal failure
- Other serious co-morbidities

Box 14.6**If the recommended targets are not achieved**

- Increase IV insulin by 1 unit/hr increments until the targets are achieved
- If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected

Action 3:

- If BG < 14mmol/l (<250 mg/dL) commence 10%glucose at 125mls/hr alongside the 0.9% saline (may need to adjust rate of 0.9% saline infusion if clinically indicated)
- And continue with insulin infusion.

Action 4:

- Monitor and replace potassium

Action 5:

- Long-acting insulin should be given to newly diagnosed patients with T1DM at a dose of 0.2-0.3 units/Kg subcutaneously to prevent rebound ketosis once they are taken off the IV insulin.

14.1.3.3. Stage 3:**6 to 12 hours****Aim:**

- Ensure that clinical and biochemical parameters are improving
- Continue IV fluid replacement appropriately
- Continue insulin administration
- Avoid hypoglycaemia
- Continue to treat precipitating factors as necessary
- Assess for complications of treatment e.g. fluid overload, cerebral oedema
- Thromboprophylaxis if indicated.

14.1.3.4. Stage 4:**12 to 24 Hours****Aim:**

- To assess whether clinical and biochemical parameters are improving or have normalized
- Continue IV fluids if the patient is not eating and drinking
- Avoid hypoglycaemia
- Continue to treat any precipitating factors as necessary
- Re-evaluate for complications of treatment e.g: fluid overload, cerebral oedema
- Thromboprophylaxis if indicated

14.1.4 Resolution of DKA

Box 14.7

Ketones less than 0.6mmol/L for 2 consecutive hours and venous pH over 7.3

- Hyperchloremic acidosis associated with large volumes of 0.9% sodium chloride will lower bicarbonate levels.
- Hence, do not use bicarbonate as a surrogate of resolution of DKA
- Urine ketone may still be present when the DKA has resolved. So do not rely on urinary ketone clearance to indicate resolution of DKA

14.1.5. Once resolution of DKA is achieved

1. Transfer to subcutaneous insulin if the patient is eating and drinking normally.
2. Start subcutaneous insulin before the IV insulin is discontinued. Ideally give the subcutaneous fast acting insulin at a meal and discontinue IV insulin one hour later.
3. In a patient who is on basal insulin, if it has been stopped in error, the insulin infusion should not be stopped until some form of background insulin has been given.
4. If the patient is not eating and drinking or has another indication for IV insulin (severe sepsis/MI) and there is no ketonaemia move to a variable rate of insulin infusion.

Box 14.8

Expectation: By 24 hours

The ketonaemia and acidosis should have normalized.

Patients should be eating and drinking

Started on basal bolus insulin regime

14.1.5.1. It is unusual for DKA not to have resolved by 24 hours with appropriate treatment.

If the above expectation is not met, need to identify, and treat the reasons for the failure to respond to treatment.

14.1.5.2. Restarting subcutaneous insulin for patients already established on insulin

The patient's previous regimen should generally be re-started if their most recent HbA1c suggests acceptable level of control i.e., HbA1c <8% (64mmol/mol)

14.1.5.3. Calculating the subcutaneous insulin dose in insulin-naïve patients

- Estimate Total Daily Dose (TDD) of insulin.
- The TDD can be calculated by multiplying the patient's weight (in kg)
 - By 0.5- 0.75 units in type 2 DM (Use 0.75 units for those thought to be more insulin resistant i.e., obese.)
 - By 0.2 to 0.5 units in type 1 DM

14.1.5.4. Calculating a Basal Bolus (QDS) Regimen:

- Give 50% of total dose- basal insulin (Glargine/Degludec/ Detemir)
- Then divide the remaining dose – Soluble Insulin/rapid acting- equally between pre-breakfast, pre-lunch and pre-evening meal.

14.1.5.5. Calculating a twice daily (BD) regimen:

If a twice daily pre-mixed insulin regimen is to be used

- Give two thirds of the total daily dose at breakfast, with the remaining third given with the evening meal.

14.2. The management of Hyperosmolar Hyperglycaemic state (HHS)

- The hyperosmolar hyperglycaemic state (HHS) is a medical emergency and has high mortality (more related to age and co-morbidities) than DKA.
- HHS is different from diabetic ketoacidosis (DKA) and treatment requires a different approach.
- Typically, occurs in the elderly
- Central pontine myelinolysis (CPM), cerebral edema and seizures are uncommon but well-known complications of HHS. Rapid changes in osmolality during treatment may be the precipitant of CPM.
- Differentiating HHS from DKA is more problematic in context of severe intercurrent illness due to increased ketosis (e.g: use of SGLT2i, fasting ketosis) and non-ketotic metabolic acidosis (e.g: AKI) and lactic acidosis.
- If predominant diagnosis is unclear (HHS v DKA v both), tailor protocol to individual patients' needs. (In patients with mixed DKA and HHS- may require a modification of this treatment guideline to take into account which aspect predominates.)

14.2.1. Differences between HHS Vs DKA

Table 14. 4: Differences between HHS vs DKA

	HHS	DKA
Age	Usually older	Usually younger
Volume depletion	10-20%	5-10%
Duration of onset	Days to weeks	Hours to days
Endogenous insulin	Present	Absent
Ketoacidosis	Absent or mild	Mild to moderate to severe

Box 14.9**Characteristic features that differentiate HHS from DKA**

- Marked hyperglycemia 540 mg/ dL (30 mmol/L) or more
- No significant hyperketonemia (<3 mmol/L) or acidosis (PH >7.3, bicarbonate >15 mmol/L)
- Osmolality (2(Na)+Glucose + urea) 320 mosmol/kg or more
- Significant dehydration and Hypovolemia

14.2.2. Goals and principles of treatment

Gradually and safely

1. Normalize the osmolality (reduce the calculated osmolality by 3-8 mosm/kg/hr)
2. Rate of fall of serum Na should not exceed 10 mmol/L / in 24 hours
3. Replace fluid and electrolyte losses (replacement may take up to 48 to 72 hours)
4. Normalize blood glucose (no more than 72-108 mg/dl/hr (4-6 mmol/L /hr) and avoid hypoglycaemia)
5. Treat the underlying cause
6. Other goals include Prevention of:
 - Arterial or venous thrombosis
 - Other potential complications e.g., cerebral oedema/ central pontine myelinolysis, foot ulcers

14.2.3. To consider HDU/ICU care

1. Osmolality greater than 350 mosmol/kg
2. Sodium above 160 mmol/L
3. Venous/arterial pH below 7.1
4. Hypokalaemia (less than 3.5 mmol/L) or hyperkalemia (more than 6 mmol/L) on admission
5. Glasgow Coma Scale (GCS) less than 12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
6. Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
7. Systolic blood pressure below 90 mmHg
8. Pulse over 100 or below 60 bpm
9. Urine output less than 0.5 ml/kg/hr
10. Serum creatinine > 200 µmol/L
11. Hypothermia
12. Macrovascular event such as myocardial infarction or stroke
13. Other serious co-morbidities

14.2.4. Management

Table 14. 5: The management of Hyperosmolar Hyperglycaemic state

Admission bloods: BG, ketones, VBG, FBC, CRP, ECG, Electrolytes, urea and creatinine, Septic screening. If indicated- CXR, Troponin I, CK, amylase, ABG

Complete initial evaluation, confirm diagnosis, treat underlying cause, and assess foot risk and ulcer prevention. Insert urinary catheter for strict hourly fluid balance.										
Fluids	Potassium	Insulin								
<p>First line treatment in HHS is fluid resuscitation.</p> <p>I.V. 0.9% NaCl as the fluid of choice to resuscitate the patient,</p> <p>Once glucose comes down <250mg /dl (<14 mmol/L), to start on 10% Dextrose infusion 125ml/hr, AND continue 0.9% NaCl</p> <p>A target blood glucose of between 180-270 mg/dL (10 and 15 mmol/L) in first 24 hours</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;"><u>Serum level</u></th><th style="text-align: center;"><u>Replacement</u></th></tr> </thead> <tbody> <tr> <td style="text-align: center;">>5.5</td><td style="text-align: center;">Nil</td></tr> <tr> <td style="text-align: center;">3.5-5.5</td><td style="text-align: center;">40 mmol per liter</td></tr> <tr> <td style="text-align: center;"><3.5</td><td style="text-align: center;">40 mmol per liter Senior review as additional potassium required</td></tr> </tbody> </table> <p>Consider the degree of initial renal impairment when correcting potassium.</p> <p>If K is 3.5 mmol/L- Hold insulin and replace Potassium and start insulin once K is > 3.5 mmol/L</p>	<u>Serum level</u>	<u>Replacement</u>	>5.5	Nil	3.5-5.5	40 mmol per liter	<3.5	40 mmol per liter Senior review as additional potassium required	<p>Insulin infusion</p> <ul style="list-style-type: none"> ➤ Start once blood glucose is no longer falling despite adequate fluid resuscitation (adequate fall of BG is between 72-108 mg/dl/hr (4-6 mmol/L/hr)) <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> ➤ Immediately, only if significant ketonaemia is present (Capillary Ketones >1 mmol/L or ketonuria (+ or more)) <p>Start fixed rate intravenous insulin infusion at 0.05 units/kg/hr</p> <p>A fall of glucose at a rate of up to 90 mg/dL (5 mmol/L) per hour is ideal.</p> <ul style="list-style-type: none"> ➤ Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse <p>Continue long acting insulin and withhold oral diabetes medications.</p>
<u>Serum level</u>	<u>Replacement</u>									
>5.5	Nil									
3.5-5.5	40 mmol per liter									
<3.5	40 mmol per liter Senior review as additional potassium required									

1. Fluid resuscitation

- Use intravenous (IV) 0.9% sodium chloride solution as the principal fluid to restore circulating volume and reverse dehydration.
- Fluid deficit is 100-220 ml/Kg
- IV fluid replacement aims to achieve a positive balance of 2-3 liters by 6 hours and 3-6 litres by 12 hours and the remaining replacement of estimated fluid losses within next 12 hours though complete normalization of biochemistry may take up to 72 hours.
- **Usual fluid replacement regime:**
 - 0-60 min - 1 L NS (more rapidly if BP is low)
 - 60 min- 6 hrs - 0.5-1 L/hr NS
 - 6- 12 hrs- ~ 0.25 L/ hour NS
 - 12-24 hrs - ~ 0.4 L/ hour NS
 - 24hrs- 72 hrs - IV fluid till SE normal and patient is eating and drinking

❖ Age, initial severity, degree of renal impairment and co-morbidities such as heart failure need to be considered during Fluid replacement.

- Once Glucose comes down <250mg /dl (14 mmol/L), to start on 10% Dextrose infusion 125ml/hr, AND continue NS

Box 14.10

Monitor

- Hourly IP/OP
- Hourly VBG , (Na), calculated osmolality , Glucose, Ketones x 6 hours, then 2 -4 hourly
- 2 hourly K for initial 6 -12 hours
- Neurology (GCS) for cerebral edema/ central pontine myelinolysis
- Lungs – pulmonary edema

2. Insulin

Start Insulin infusion

- Once blood glucose is no longer falling despite adequate fluid resuscitation (adequate fall of BG is between 72-108 mg/dl/hr (4-6mmol/L/hr)
OR
- Immediately, only if significant ketonaemia is present (Capillary Ketones >1 mmol/L or ketonuria (++) or more))

❖ Start fixed rate intravenous insulin infusion at 0.05 units/kg/hr

- If glucometer reads “blood glucose as “Hi”, venous blood should be sent to the laboratory hourly or measured using VBG until the bedside meter gives exact value
- A fall of glucose at a rate of up to 90 mg/dL (5 mmol/L) per hour is ideal.
- Avoid hypoglycaemia.

- Target BM is between **180-270 mg/dL (10 and 15 mmol/L) in first 24 hours.**
- Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse

❖ **Continue long-acting insulin and withhold oral diabetes medications.**

- If BM do not drop, adjust insulin by 1 unit/hour increments to achieve targets
- If K is 3.3 mmol/L - Hold insulin and replace Potassium and start insulin once K is > 3.5 mmol/L

3. Na+

- Fluid replacement alone (without insulin) will lower blood glucose which will reduce osmolality causing a shift of water into the intracellular space. This inevitably results in a rise in serum sodium (**a fall in blood glucose of 99 mg/dL (5.5 mmol/L) will result in a 2.4 mmol/L rise in sodium**).
 - ❖ **This is not necessarily an indication to give hypotonic solutions.**
- **Rising sodium is only a concern if the osmolality is NOT declining concurrently.**
- The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.
- Target osmolality drop - calculated osmolality by 3-8 mOsmol/kg in first hour and 3 mOsmol/kg/hour thereafter
- If the inevitable rise in serum Na⁺ is much greater than 2.4 mmol/L for each 99 mg/dL (5.5 mmol/L) fall in blood glucose, this would suggest insufficient fluid replacement. Therefore, increases the fluid replacement.

When to use hypotonic solution

- ❖ **Only switch to 0.45% sodium chloride solution if the osmolality is not declining despite adequate positive fluid balance AND adequate rate of fall of plasma glucose is not being achieved.**
- If osmolality is falling at a rate exceeding 8 mosmol/kg/hr consider reducing the infusion rate of IV fluids and/or insulin (if already commenced).

4. Potassium

- **If potassium is <3.5 mmol/L- replace potassium up to 3.5 mmol/L before starting insulin**
- **Life threatening hypokalemia can occur with insulin infusion due to precipitous falls upon treatment with intravenous insulin**
- **Regular monitoring of potassium is mandatory**
- **Cardiac monitoring is mandatory If K + infusion is greater than 20mmol/hour**
- Potassium replacement must be done cautiously if renal function remains depressed and/or urine output does not increase at least to 0.5ml/kg/hour.

5. Complication of treatment

- Assessment for complications of treatment e.g., fluid overload, cerebral oedema or central pontine myelinolysis (as indicated by a deteriorating conscious level) must be undertaken frequently (every 1-2 hours).

6. Treat the precipitating cause appropriately

7. Anticoagulation

- Patients in HHS have an increased risk of arterial and venous thromboembolism
- All patients should receive prophylactic low molecular weight heparin (LMWH) for the full duration of admission unless contraindicated. (1 mg/kg dose daily or 0.5mg/Kg daily dose if eGFR is <30)

Other electrolyte imbalances and complications associated with HHS

- Hypophosphatemia and hypomagnesaemia are common in HHS.
- As with the management of DKA there is no evidence of benefit of treatment with phosphate infusion.
- However, these patients are often elderly and may be malnourished, and the refeeding syndrome could be precipitated once the person begins to eat.
- Routine check is not recommended.
 - ❖ But need to check – in the presence of **Cardiac dysfunction, haemolytic anaemia, respiratory depression, hypocalcaemia or suspecting re-feeding syndrome**
- If hypophosphatemia persists beyond the acute phase of treatment of HHS or presence of above factors, oral or IV replacement should be considered.
- Magnesium replacement has also not been shown to be beneficial so should only be considered if the patient is symptomatic or has symptomatic hypocalcemia.

14.2.5. When to discontinue IV insulin and Fluids

- Resolution of HHS may take up to 72 hours
- **Once the patient is mentally alert + Osmolality < 315mOsm/L + can eat orally → switch IV insulin to s/c insulin (the regime being determined by individual circumstances).**
 - But IV fluids may be required for longer if intake is inadequate.
 - Maintain IV insulin infusion for 1 hour after starting subcutaneous insulin.
 - Change to variable rate insulin infusion (VRIII) 24 hours later, if still not eating and drinking.
 - For patients with previously undiagnosed diabetes or well controlled on oral agents, switching from insulin to the appropriate oral hypoglycaemic agent should be considered after a period of stability (weeks or months).
 - All patients will require diabetes education to reduce the risk of recurrence and prevent long-term complications.

14.3 Management of Hypoglycaemia in Adults with Diabetes Mellitus

Hypoglycaemia is the most harmful acute complication in patients with diabetes especially those who are receiving insulin or sulfonylurea.

- **Other drugs used to treat DM are less likely to cause hypoglycaemia.**
- **Particularly elderly patients or those with renal impairment are at risk.**

14.3.1 Definition

Hypoglycaemia in a patient with diabetes is defined as blood glucose concentration less than 70 mg/dL (4 mmol/L). The symptoms of hypoglycaemia vary between individuals. In healthy individuals, symptoms of hypoglycaemia develop at a mean plasma glucose concentration of approximately 55 mg/dL (3 mmol/liter). However, the glycemic thresholds for this and other responses to hypoglycaemia shift to lower plasma glucose concentrations in patients with recurrent hypoglycaemia.

14.3.2. Clinical symptoms

Hypoglycaemia causes autonomic and neuroglycopenic symptoms.

Autonomic symptoms (blood sugar <55 mg/dL (3.1 mmol/L)) are tremor, palpitation, sweating and paresthesia. Drowsiness, delirium, confusion, seizure and coma are considered as neuroglycopenic symptoms and usually occur when blood sugar is less than 50 mg/dL (2.8 mmol/L).

➤ Prolonged hypoglycaemia may lead to permanent neurological deficits.

Impaired awareness of hypoglycaemia (IAH)

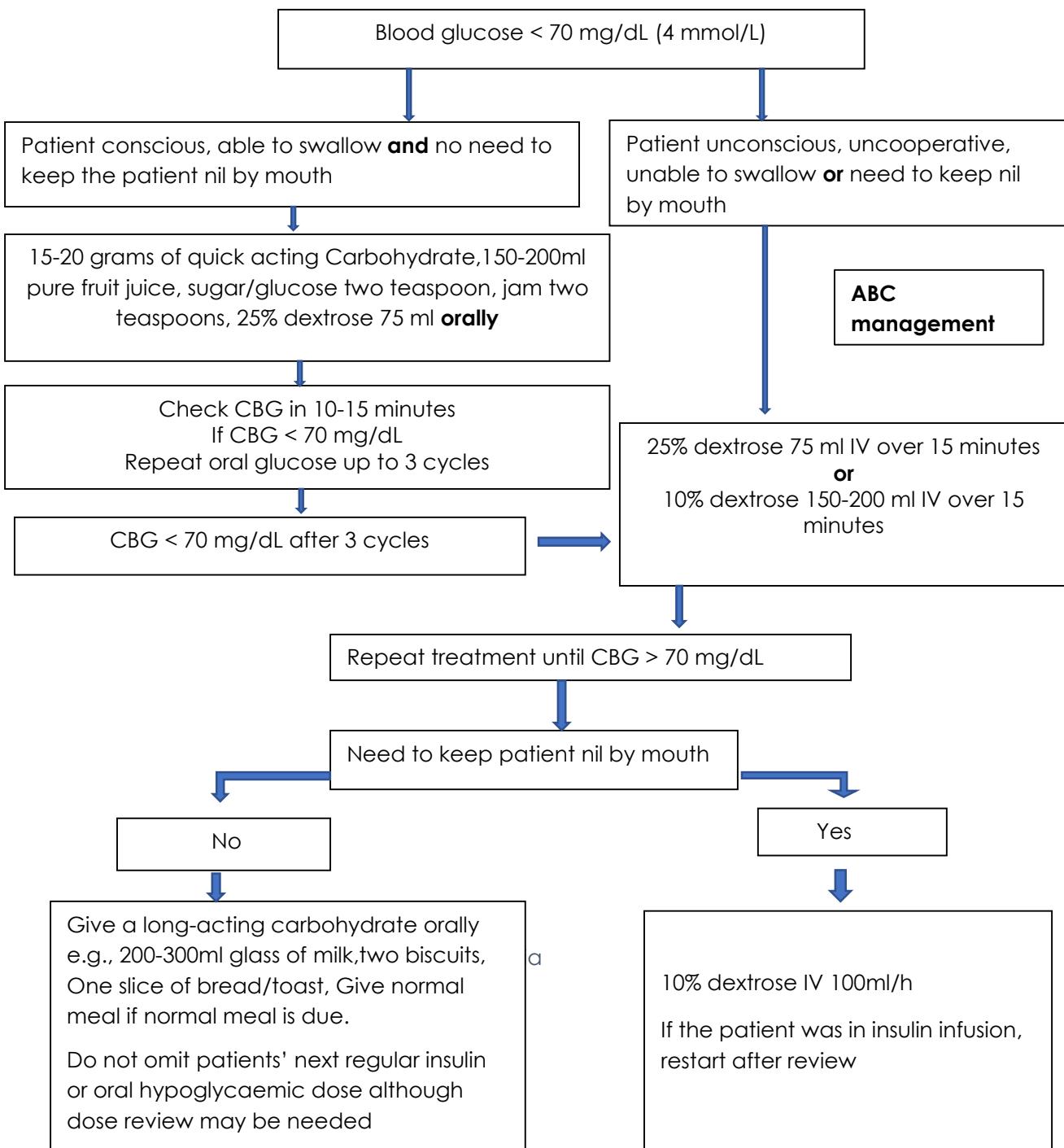
IAH results in the warning symptoms of hypoglycaemia becoming diminished in intensity, altered in nature or lost altogether.

This increases the susceptibility of affected patients of progression to severe hypoglycaemia. The risk of IAH increases with duration of diabetes, its control and type of DM. It is more common in type 1 than in type 2 diabetes.

14.3.3. Management

- Reducing the risk of hypoglycaemia by patient education, frequent self-monitoring of blood glucose, individualized glycemic goals, flexible and rational insulin (and other drug) regimens, and ongoing professional guidance.
- Hypoglycaemia should be treated as an emergency irrespective of level of consciousness.
- Way of treatment may depend on the severity of hypoglycaemia.

Management of Hypoglycaemia



❖ **If IV access not available or not responding to IV glucose**

- Give 1mg Glucagon IM if available.

Figure 14. 2 Management of hypoglycaemia

Glucagon

- IM Glucagon may be less effective in patients under influence of alcohol or in patients on sulfonylurea therapy
- It may take upto 15 minutes to work.
- Repeated administration of glucagon is not recommended
- Glucagon is not suitable for patients who are starved or have severe hepatic disease
- If the patient is unable to swallow- need NG feeding
- DO NOT omit insulin injection if due and may need dose adjustment
- Patients who self-manage their insulin pumps (CSII)
 - May not need a long-acting carbohydrate
 - Adjust the pump settings appropriately.

❖ **If the hypoglycaemia was due to sulfonylurea or long-acting insulin therapy,**

- Can have persistent hypoglycaemia up to 24-36 hours following the last dose especially if there is concurrent renal impairment and in elderly
- Regular capillary blood glucose monitoring is recommended for at least 24 to 48 hours.

❖ **If the patient was on IV insulin**

- Restart infusion once blood glucose above 63 mg/dL (3.5mmol/L) after reviewing the dose
- Consider concurrent IV 10% glucose infusion at 100ml/hr or stepping down to variable scale if appropriate.

If the patient is 'nil by mouth'

Consider intravenous infusion of 10% glucose at a rate of 100ml/hr. May continue until the patient is no longer nil by mouth.

Chapter 15

Management of diabetes in special situations

15.1 Diabetes in Pregnancy

Introduction and Classification of Diabetes in Pregnancy

- Pregnancy can be associated with varying degrees of insulin resistance due to secretion of diabetogenic hormones from the placenta and insufficient secretion of insulin from the pancreatic β cells, leading to significant derangements of glucose tolerance. The blood sugar control of already existing diabetes mellitus can be deranged during the pregnancy. Above changes may lead to development of gestational diabetes mellitus (GDM) after the first trimester.
- GDM accounts for 90% of diabetes in pregnancy. Prevalence of GDM in pregnancy is 5.7 %, while the prevalence of both GDM and pregestational diabetes is 7.1% in Sri Lanka. Diabetes in pregnancy leads to poor maternal, foetal, and neonatal outcomes which causes significant morbidity and mortality.
- Women with GDM are at higher risk of cardiovascular mortality, coronary artery disease (CAD) and development of T2DM in later life.

Classification of Diabetes in Pregnancy

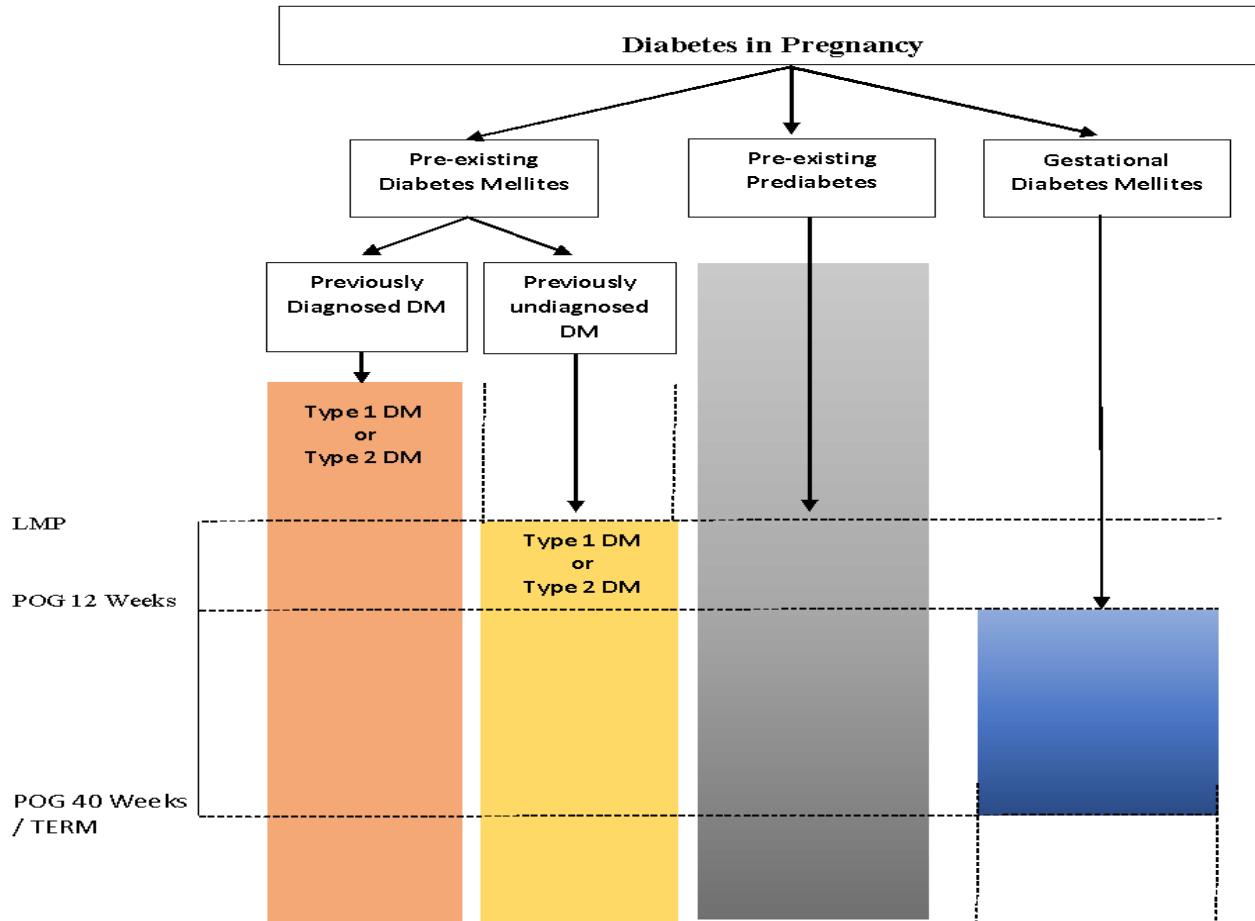


Figure 15 1: Classification of diabetes in pregnancy

15.1.1 Diabetes in pregnancy: preconception care

Avoidance of teratogenic drugs and being normoglycaemic during the period of conception can improve the maternal and neonatal outcomes.

- It is recommended to stop all medications contraindicated in pregnancy if reliable contraception method is not being practiced.
E.g:
 - All oral hypoglycaemic drugs except metformin.
 - ACE inhibitors / angiotensin receptor blockers (ARB),
 - Statins
- It is recommended to screen all women planning for pregnancy with fasting plasma glucose (FPG), and / or HbA1c, prior to conception.

15.1.1.1 Woman with previously undiagnosed DM proceeding to pregnancy:

Women who attend the booking visit should be screened for undiagnosed DM and prediabetes.

The criteria to detect undiagnosed diabetes mellitus (DM) at the booking visit (within the first trimester) are as follows

- **FPG \geq 126 mg/dL with symptoms OR,**
- **Random plasma glucose (RPG) \geq 200 mg/dL with symptoms OR,**
- **HbA1c \geq 6.5 %**

Recommendation

- Every pregnant woman should be screened for DM and prediabetes at the booking visit.

Even patients with borderline diabetes may have falsely low plasma glucose values due to vomiting, loss of appetite and increased delivery of blood glucose to the foetus. Therefore, 75g OGTT is indicated for patients with high risk of GDM and suspected prediabetes.

Recommendation

A 75 g, two-hour Oral Glucose Tolerance Test (75 g OGTT) is indicated at the booking visit, if following are present

- FPG between 90 – 125 mg/dL.
- 2 Hour post prandial plasma glucose (PPPG) \geq 120 mg/dL.
- Presence of risk factors for GDM. (Ref 15.1.2)
- History of prediabetes. (FPG 100 mg/dL to 125 mg/dL or impaired glucose tolerance in a previous 75g OGTT).
- HbA1c 5.7% – 6.4 %.
- History of poor obstetric outcome in a previous pregnancy.

15.1.1.2 Woman with Pre-existing Diabetes proceeding to pregnancy:

Women with diabetes mellitus, who are planning to become pregnant, would be benefitted by maintaining FPG 90 – 100 mg/dL, pre-meal plasma glucose level of 72 – 100 mg/dL, and 2-hour PPPG $<$ 120 mg/dL.

Women with pre-existing diabetes would be ideally managed by a multidisciplinary team including an obstetrician, physician, endocrinologist, nutritionist, and a diabetes educator, when available.

Recommendation

- Pre-conception counseling is recommended, stressing the importance of optimal glycaemic control and optimizing the treatment plan, to minimize poor obstetric outcome.
- Effective and reversible contraception is beneficial, until the HbA1c level is $<$ 6.5 % and the treatment plan is optimized prior to conception.

- Establish optimal blood glucose control prior to conception, using metformin and / or Insulin, in patients already diagnosed with DM. Stop all other oral hypoglycaemic drugs. Target HbA1c should be < 6.5%.

Women with established DM related complications can progress further during pregnancy.

Recommendations

- Referrals for diabetes related cardiovascular, renal and ophthalmic complications are beneficial when appropriate.
- Adequate renal assessment with quantification of albuminuria, and serum creatinine before discontinuing contraception is necessary.
- A referral to a nephrologist should be done before discontinuing contraception, if the urinary protein: creatinine ratio is greater than 30 mg/Cr mmol or serum creatinine is elevated above normal and/ or the estimated glomerular filtration rate (eGFR) is less than 45 ml/minute/1.73 m
- Ophthalmological screening- Refer to 12.1.6.5

15.1.2 Diabetes in pregnancy: Antenatal Care

Antenatal care in diabetes in pregnancy aims to optimize good maternal and foetal outcomes. Screening and follow-up of pregnant women in the obstetric clinic should be geared to identify women with DM, prediabetes and GDM and related complications in pregnancy.

Recommendation

- It is recommended to take a complete history at the antenatal visit to cover following components: past medical history, obstetric conditions, lifestyle, diet, compliance to drugs and risk factors for GDM.
- If any of the following risk factors for GDM are found, plan for a 75g OGTT at the booking visit, which are:
 - BMI > 30 Kg/m²
 - Previous macrosomic baby, weighing ≥ 4.0 kg,
 - History of GDM in a previous pregnancy
 - Diabetes in a first-degree relative
 - History of prediabetes (impaired glucose tolerance / impaired fasting glucose)
 - History of poor obstetric outcome in a previous pregnancy
- FPG after 8 hours fast and/or 2-h PPPG and / or HbA1c should be done, in a mother having risk factors for GDM, if the 75g OGTT is not possible at the booking visit during the first trimester.
- HbA1c can be done during the first trimester, to assess the previous glycaemic control and to identify the potential risk for complications, in a woman already diagnosed with DM. (Target HbA1c < 6.5%)

15.1.2.1 Diagnosis of GDM

GDM is defined as, carbohydrate intolerance of variable severity, having its onset during the second or third trimester of pregnancy, which returns to normalcy after delivery. All pregnant women are routinely screened for the presence or development of risk factors for GDM, and it is documented in the pregnancy record in each clinic visit.

Recommendation

- All the mothers without history of DM or GDM within the present pregnancy, should undergo 75 g, 2-h OGTT between 24 to 28 weeks (or at 26 weeks)
- If there is a past history of GDM, it is recommended to perform 75g 2-h OGTT at 18 weeks, even if the FPG/PPPG or 2-h OGTT at the booking visit are normal
- If there is a past history of GDM with or without risk factors, 75g 2-h OGTT can be repeated in the third trimester at 34 weeks, even though the 2-h OGTT values are continuously normal at 18 weeks and at 24 to 28 weeks of POG
- HbA1c is not recommended to diagnose GDM.

Diagnosis of GDM is made if one or more threshold values are exceeded in the 75g OGTT (FPG \geq 92 mg/dL, or 1-h value \geq 180 mg/dL or 2-h value \geq 140 mg/dL), after the first trimester.

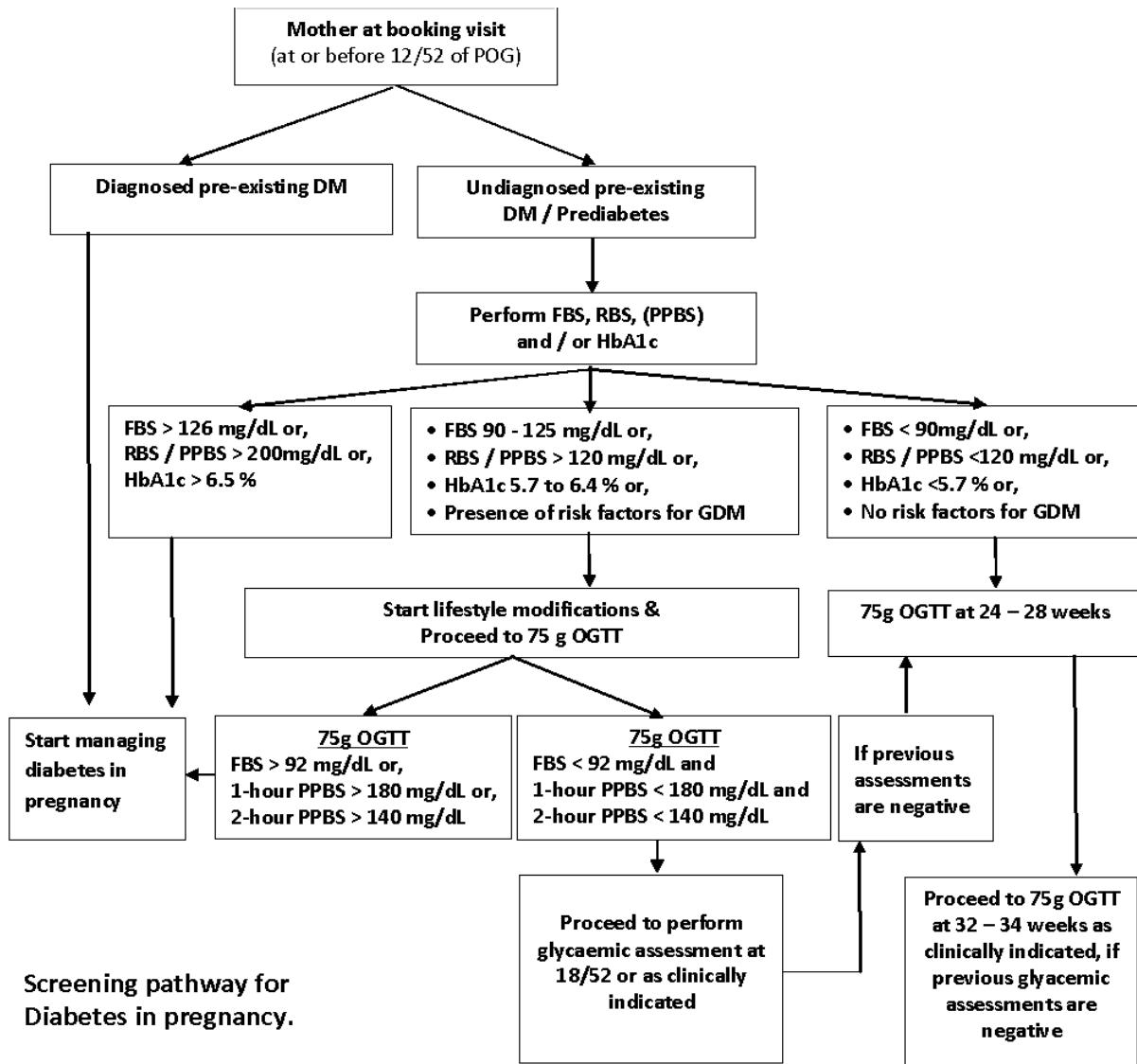


Figure 15.2 Screening pathway for diagnosis of pregnancy

15.1.2.2 Antenatal Blood sugar monitoring and control

Self-monitoring of blood glucose (SMBG) has been recommended to achieve optimal blood glucose control, especially for women on insulin therapy.

In diabetes in pregnancy, plasma glucose targets are as follows:

1. FPG < 95 mg/dL
2. 1-h postprandial plasma glucose < 140 mg/dL
3. 2-h postprandial plasma glucose < 120 mg/dL

Recommendation

- Blood Sugar Series (BSS) with FPG and 2-h PPPG after three main meals are recommended for monitoring glycaemic control.
- Frequency of doing BSS and pre-prandial plasma glucose testing, should be decided by the treating obstetrician or physician.

15.1.2.3 Non-pharmacological management of diabetes in pregnancy

Non-pharmacological management includes dietary control (medical nutrition therapy), regular exercises and stress reduction.

The dietary composition having 45-55% carbohydrates, 15-20% protein and 20-30 % fat with less than 10% of saturated fat from total daily calorie requirement is recommended. The type and amount of carbohydrate has to be adjusted to control postprandial plasma glucose level. Frequent smaller meals evenly spaced throughout the day, with less than 10-12 hours fasting in-between are recommended.

Following calorie intake is recommended, depending on the present pregnant weight of the patient:

- **Underweight** : 40 Kcal / present pregnant weight (Kg) / day
- **Normal weight** : 30 Kcal / present pregnant weight (Kg) / day
- **Overweight** : 24 Kcal / present pregnant weight (Kg)/ day
- **Obese** : 12-15 Kcal / present pregnant weight (Kg) / day

Recommendation

- It is recommended to start lifestyle modification and medical nutrition therapy (MNT) by the nutritionist /qualified personnel soon after the diagnosis of diabetes or prediabetes is made. Adequate review with follow up is required.
- A tailor-made dietary plan for each pregnant mother with diabetes or GDM, is beneficial to achieve normoglycaemia.
- It is recommended to introduce a planned physical activity at least 30 minutes per day depending on the patient's physical capacity.
- While doing exercises, excessive abdominal muscular contraction should be avoided.
- Exercise should not be recommended in the presence of medical or obstetric contraindications.

15.1.2.4 Pharmacological management of diabetes in pregnancy

- Both insulin and metformin are recommended for treatment of diabetes in pregnancy (pre-gestational DM /GDM), as pharmacological therapy.
- At the time of diagnosis, Insulin should be started as the first line treatment together with MNT, if FPG is ≥ 126 mg/dL, or 75g 2h OGTT value ≥ 180 mg/dL, or 2-h PPPG in BSS ≥ 140 mg/dL. Metformin can be started together with MNT, if FPG is 100 – 125 mg/dL and 75g 2-h OGTT value is 140-179 mg/dL. Non-pharmacological management alone can be started if FPG is between 92 – 99 mg/dL and 2-h OGTT value is 120 – 139 mg/dL.
- All types of insulin including regular insulin, rapid acting analogue insulin, intermediate acting insulin (Isophane/NPH insulin), long-acting insulin and pre-mixed insulins, can be used in pregnancy. Out of rapid acting insulins, insulin aspart and Insulin lispro are safe. Out of long-acting insulin analogues, Insulin detemir can be used. There is not adequate safety data for use of Insulin glulisine, glargine and degludec.
- Required initial dose of insulin can be 0.2 – 0.5 U/Kg/day. Insulin dose regimen has to be titrated to achieve target postprandial and fasting plasma glucose levels (target 2-h PPPG is ≤ 120 mg/dL and FPG is ≤ 95 mg/dL). It is recommended to give a premeal short acting insulin (regular insulin or rapid acting insulin analogue) three times per day before each main meal to achieve post meal targets. Basal insulin (insulin detemir) or Intermediate acting insulin (isophane insulin), at night can be given to control fasting hyperglycaemia.
- In general, pre-mixed insulin is not preferred in pregnancy, because the post meal target of PPPG ≤ 120 mg/dL, may be difficult to achieve, with pre-mixed insulin alone, especially after lunch.
- Pre-mixed insulin may be considered on individual basis; if the woman rejects basal bolus regimen or if the blood sugar control is satisfactory throughout, with pre-mixed insulin, from the pregestational period.

Recommendation

- Pharmacological treatment should be started, if blood sugar control is not achieved with MNT and physical activity alone.
- Women with T1DM and T2DM should be started on low-dose aspirin 60–150mg/day (usual dose 81 mg/day) from the end of first trimester up to term, to prevent preeclampsia.
- If the mother is on metformin, due to polycystic ovary syndrome and pregnancy following induced ovulation, it may be discontinued by the end of the first trimester, if there is very clear evidence of normoglycaemia in pregnancy, having HbA1c < 5.5 %.

15.1.2.5 Monitoring fetal growth and wellbeing

Recommendation

- At 20 weeks of gestation, foetal anomaly scan would be beneficial.
- From 28 to 36 weeks of gestation, serial ultrasound monitoring of foetal growth and amniotic fluid volume assessment should be done monthly.
- Before 28 weeks, routine monitoring of foetal wellbeing is not recommended unless there is intrauterine growth restriction.

- In a pregnant woman with diabetes, new onset hypertension (blood pressure \geq 140/90 mmHg) or development of significant proteinuria, should be evaluated and treated as per the management of hypertension in pregnancy guideline.

15.1.3 Intrapartum Care

Mode of delivery and time of delivery should be reviewed by the Obstetrician at 36-37 weeks of gestation. If the glycaemic control is optimum without foetal and maternal complications, pregnancy can be extended up to 40 weeks of gestation, but not beyond. If poor pregnancy outcome is noted in a woman with diabetes in current pregnancy, early delivery is considered.

Recommendation

- Diabetes in pregnancy alone, is not an indication for a caesarean section.
- Assessment for anaesthesia should be done in advance if diabetes in pregnancy is associated with maternal and foetal complications or having co-morbid conditions.
- If elective delivery is indicated in a woman with diabetes in pregnancy, it should be considered before 39 weeks.

15.1.3.1 Preterm labour in women with diabetes

Women with diabetes who receive steroids for foetal lung maturation can have acute blood glucose fluctuations. Therefore, stringent blood glucose monitoring and adjusting the treatment regimen may be required.

Recommendation

- Diabetes in pregnancy is not a contraindication for antenatal steroids given for foetal lung maturation or for tocolytics.

15.1.3.2 Care at the time of Delivery

Intrapartum random plasma glucose level at the time of delivery, should be between 72-125 mg/dL. If the patient is on metformin and / or MNT alone, plasma glucose monitoring can be done 4-6 hourly. If the patient is on Insulin, hourly plasma glucose monitoring may be useful. If LSCS is carried out, plasma glucose should be monitored in every 30 to 60 minutes intervals. If the glycemic targets are out of control, starting IV insulin infusion with IV dextrose and hourly monitoring of plasma sugar may be required.

15.1.4 Postnatal Care

15.1.4.1 Breastfeeding recommendation

All types of insulin can be used during the antenatal period and metformin can be safely used in lactating women. All oral hypoglycaemic drugs, except metformin, are contraindicated during breastfeeding.

Recommendation

- Start breastfeeding immediately after delivery and continue if not contraindicated due to other reasons.

15.1.4.2 Pharmacological treatment following delivery

Insulin resistance and requirement decreases dramatically immediately after delivery. Therefore, pharmacological treatment can be adjusted as follows for women with diabetes in pregnancy.

Table 15. 1: Pharmacological treatment following delivery

	Immediate Postpartum intervention
Metformin alone	Stop Metformin
Insulin < 0.5 IU/Kg/day	Stop Insulin
Insulin 0.5 to 1 IU/Kg/day	Decide the dose on individual basis
Insulin > 1 IU /Kg/day	Reduce 50% from the antenatal Insulin requirement

Postpartum plasma glucose should be monitored and need to be well controlled prior to discharge from the hospital.

15.1.5 Follow-up Care

Women with pre-existing diabetes should be referred back to their routine diabetes care arrangements. Women with a history of GDM appear to have a nearly 10-fold higher risk of developing T2DM than those with a normoglycaemia during pregnancy. Therefore, women with a history of GDM should undergo screening for T2DM or prediabetes at least yearly. Women with a history of GDM or diabetes should be educated on appropriate contraception and the importance of maintaining normoglycaemia for future pregnancies.

Recommendation

- Arrange FPG or 75g OGTT after 6 to 8 weeks postpartum, for mothers with GDM.
- Women with a history of GDM who are found to have prediabetes, 6–8 weeks after delivery should receive intensive lifestyle interventions and metformin to prevent diabetes.
- A referral to a medical clinic should be done to screen for non-communicable diseases and to assess the cardiovascular risk in regular intervals

15.1.5.1 Family planning

All reversible or permanent and reliable family planning methods can be used.

15.2. Diagnosis and Management of the Metabolic Syndrome

- Metabolic syndrome is a collection of metabolic risk factors that appears to directly promote the development of atherosclerotic cardiovascular diseases (ASCVD) and T2DM.
- Most widely recognized risk factors are atherogenic dyslipidemia (increased triglycerides and apolipoprotein B levels, increased small LDL particles and low HDL levels), increased plasma glucose levels and high blood pressure.
- Treating metabolic syndrome is a secondary target in reducing cardiovascular events. Smoking cessation, lowering the levels of LDL-C, and blood pressure management are primary targets for risk reduction.

15.2.1. Underlying Risk Factors for metabolic syndrome

- Obesity – Visceral and upper body obesity has greater risk of developing metabolic syndrome and insulin resistance
- Physical inactivity
- Aging
- Hormonal imbalances
- Genetic factors
- Environmental factors
- Increased consumption of atherogenic diet

15.2.2. Criteria for Clinical Diagnosis of metabolic syndrome

Meet any 3 out of 5 criteria

1. Elevated waist circumference: (men $\geq 90\text{cm}$, women $\geq 80\text{cm}$)
2. Elevated triglycerides: [$\geq 150\text{mg/dL}$ (1.7mmol/L) or on treatments for high triglyceride]
3. Reduced HDL-C: Men $< 40\text{mg/dl}$ (1.03 mmol/L), women $< 50\text{mg/dL}$ (1.3 mmol/L)
Or taking treatments for reduced HDL-C levels
4. Elevated blood pressure: $\geq 130\text{ mmHg}$ systolic BP or $\geq 85\text{ mmHg}$ diastolic BP
Or on antihypertensive drug treatment in a patient with a history of hypertension
5. Elevated fasting glucose: $\geq 100\text{ mg/dL}$ or on drug treatment for elevated glucose

15.2.3. Clinical Management of the metabolic syndrome

Goals of Clinical Management

1. Prevention of ASCVD
2. Prevention of subsequent development of T2DM

15.2.4. Therapeutic Targets and Recommendations for Clinical Management of metabolic syndrome.

15.2.4.1. Lifestyle risk factors

15.2.4.1.1. Abdominal obesity

Targets:

- Reduce body weight by 7% to 10% during first year of therapy (Ideally 5-10% in 3-6 months).
- Continue weight loss thereafter to achieve ultimate desirable weight (BMI <23 kg/m²)

Recommendations:

- Consistently encourage weight maintenance/reduction through appropriate balance of physical activity and caloric intake. Encourage to participate in formal behavior-modification programmes when indicated to maintain/achieve waist circumference of <90cm men and <80cm in women.
- Aim initially at slow reduction of BW 7% to 10% from baseline weight.

15.2.4.1.2. Physical inactivity**Targets:**

Regular moderate-intensity physical activity; at least 30 min of continuous or intermittent (and preferably >60 min) 5 days/week, but preferably daily (150min/week)

Recommendations:

In patients with established CVD, assess risk with detailed physical activity history and/or an exercise test, to guide prescription.

Encourage 30 to 60 min of moderate-intensity aerobic activity: brisk walking and increase in daily lifestyle activities (e.g., pedometer step tracking, walking breaks at work, gardening and housework).

Longer exercise times can be achieved by accumulating the time slots of exercise throughout the day.

Encourage resistance training 2 days/week. Advice medically supervised programs for high-risk patients (e.g: recent acute coronary syndrome or revascularization, CHF).

15.2.4.1.3. Atherogenic diet

Reduced intake of saturated fat *trans*-fat, cholesterol

Recommendations:

- Saturated fat <7% of total calories; reduce *trans*-fat; dietary cholesterol <200 mg/dL; total fat 25% to 35% of total calories.
- Most dietary fat should be unsaturated.
- Simple sugars should be limited.

15.2.4.2. Metabolic risk factors**15.2.4.2.1. Atherogenic Dyslipidemia** – refer to guidelines on management of dyslipidaemia in secondary and tertiary care.

15.2.4.2.2. Elevated Blood pressure – refer to guidelines on management of hypertension in secondary and tertiary care.

15.2.4.2.3. Elevated blood sugar levels

Targets:

For patients with IFG, delay progression to T2DM.

Recommendations:

- For IFG, encourage weight reduction and increased physical activity.
- Metformin therapy may be used for prevention of diabetes in those with metabolic syndrome and prediabetes with obesity or those with previous GDM.

15.2.4.2.4. Prothrombotic state

People with the metabolic syndrome typically manifest elevations of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors.

Targets:

Reduce thrombotic and fibrinolytic risk factors.

Recommendations:

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with established atherosclerotic cardiovascular disease. Refer to chapter 11

15.2.4.2.5. Proinflammatory state

Metabolic syndrome frequently has a proinflammatory state as shown by elevated cytokines (e.g., tumor necrosis factor- and interleukin-6) and acute-phase reactants (CRP, Fibrinogen)

Recommendations - lifestyle therapies

15.3 Management of Diabetes Mellitus (Type 2) in Heart Failure

15.3.1 Introduction

Diabetes mellitus (DM) and heart failure (HF) often occur concomitantly, and each disease independently increases the risk for the other.

The prevalence of diabetes mellitus ranges from 10%-47% in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)

DM is associated with increased incidence of heart failure which is higher in women than men. It is also an important predictor of the development of symptomatic heart failure in patients with asymptomatic left ventricular (LV) dysfunction.

Poor glycemic control is associated with greater risk for the development of HF; for each 1% increase in HbA1c the risk of incident HF increases by 8% to 36%.

Identifying and implementing optimal treatment strategies for patients living with DM and HF is critical to improve the outcomes in this high-risk population.

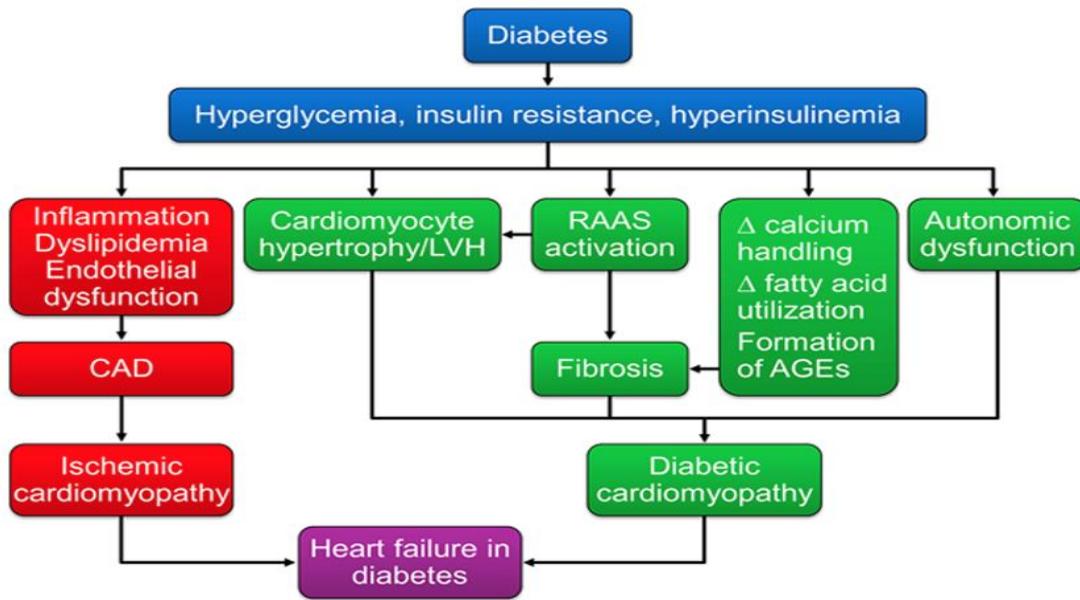
Box 15.1

Risk factors for increased incident HF

- Older age
- Coronary Artery Disease (CAD)
- Peripheral arterial disease
- Nephropathy
- Retinopathy
- Longer duration of DM
- Obesity
- Hypertension
- Higher NT-proBNP (N-terminal pro-B-type natriuretic peptide)

15.3.3 Pathophysiology of heart failure in diabetes mellitus

DM can contribute to the development of structural heart disease and HF via systemic, myocardial, and cellular mechanisms (figure 15.3.1)



15.3: Pathophysiology of heart failure in Diabetes Mellitus

The hyperglycemia, insulin resistance and hyperinsulinemia that often present in diabetes mellitus trigger a cascade of deleterious effects that contribute to the development of heart failure in diabetes mellitus. (AGEs- advanced glycation end products; CAD- coronary artery disease; LVH- left ventricular hypertrophy, RAAS- renin-angiotensin-aldosterone system.).

15.3.4 Glycemic Goals in Patients with DM and HF (fig 15.3.2)

The incidence of Heart failure is increased with patients with hyperglycemia with or without DM, however the available data suggest that intensive glycemic control in patients with DM does not reduce the risk.

In terms of management of DM in established Heart Failure, it is now more focused on the cardiovascular safety of glucose lowering drugs than the potential benefits of lower HbA_{1c} targets.

The association between HbA_{1c} and mortality among patients with HF is consistently U shaped, with the lowest mortality in patients with HbA_{1c} 7% to 8%.

Table 15. 2: Hemoglobin (HbA1C) goals in patients with Diabetes Mellitus and Heart Failure

<ul style="list-style-type: none"> Patient's clinical /functional status Self-management capacity Social support Medication side effects and costs Hypoglycaemia risks Treatment burden 			
6.5%	7.0%	8.0%	8.5%
<ul style="list-style-type: none"> Long life expectancy Stage A, B or C Heart failure No Serious Comorbidities No Serious diabetes Complications No medication side effects/ hypoglycaemia or treatment burden 	<ul style="list-style-type: none"> Intermediate life expectancy Stage C Heart failure Stage D heart failure with and /or considering advanced therapies (LVAD, transplant) Micro/macrovascular diabetes complications Severe hypoglycaemia Polypharmacy/high treatment burden 	<ul style="list-style-type: none"> Limited life expectancy Stage D Heart failure End Stage kidney disease Oxygen-dependent Lung disease Uncontrolled cancer Advanced dementia 	HbA1c>8.5% May lead to Symptomatic hyperglycemia

The HbA1c goal should be individualized in patients with heart failure and diabetes mellitus based on the patient's clinical/functional status, hypoglycaemic episodes, self-management capacity and family support system(LVAD- left ventricular assist device)

15.3.5 Hypoglycaemic agents and its choice in heart failure

15.3.5.1. Metformin

Metformin was previously contraindicated in HF because of concerns regarding the rare risk of lactic acidosis. However, its benefits are more in favor of its use. Metformin was associated with following benefits:

1. Reduced mortality and reduction in all -cause hospitalization in patients with HF.
2. Initiation of metformin was associated with lower risk of HF hospitalization than sulfonylurea drugs
3. There are some observations of metformin-associated reductions in macrovascular events, including Myocardial infarction (MI) and all-cause mortality.

In light of these findings, the FDA removed HF as a contraindication to metformin use in 2006. It is reasonable to use metformin in patients with DM at risk of or with established HF.

Recommendations

- Metformin can be continued or initiated in stable HF in a patient with diabetes.
- Metformin should be discontinued in patients presenting with decompensated heart failure (cardiogenic shock/pulmonary edema/sepsis) which will increase the risk of lactic acidosis.
- Metformin can be restarted when the patient is clinically stable.

15.3.5.2 Sodium-glucose co-transporter-2 (SGLT-2) inhibitors

- These are the first class of glucose-lowering agents demonstrated to reduce the risk of HF hospitalization and mortality in patients with DM.
- It is reasonable to consider SGLT-2 inhibitor use as part of a prevention strategy in patients with DM at high risk for HF.
- SGLT-2 inhibitors are also a good glucose-lowering medication choice in patients with established HF and DM.
- Cardiovascular benefits of SGLT-2 inhibitors should be balanced with their potential risks of adverse effects.

Recommendations

- It is recommended to initiate with SGLT2 inhibitors with proven benefit in heart failure (canagliflozin dapagliflozin empagliflozin) in patients with established heart failure in addition to metformin. SGLT2 inhibitors with proven cardiovascular benefit may be used in patients with risk of heart failure for prevention of heart failure.

15.3.5.3 Sulfonylurea Drugs

Use of metformin and SGLT-2 (sodium glucose cotransporter type 2) inhibitors (see SGLT2 Inhibitors), is preferable to sulfonylurea drugs in patients at high risk for HF and those with established HF.

Recommendations

- If sulfonylureas are needed to achieve glycemic control in addition to metformin and SGLT2 inhibitors, newer sulfonylureas such as Glimepiride and Gliclazide are preferred.

15.3.5.4 Insulin

The use of insulin in patients with DM and Heart Failure is associated with conflicting evidence. Some observational studies and subgroup analyses of clinical trials have demonstrated that insulin use is associated with greater risk of death in patients with DM and HF.

However, insulin is sometimes required to achieve adequate glycemic control in individuals with DM and HF.

Recommendations

- It should be used with caution. (Risk of weight gain and hypoglycaemia) Other agents, such as metformin and SGLT-2 inhibitors, are preferred if adequate glycemic control can be achieved without insulin.
- In decompensated heart failure Insulin is preferable over the oral hypoglycaemic drugs to achieve glycemic control.
- When glycemic control cannot be achieved with metformin and SGLT2 inhibitors, or when those are contraindicated, Insulin can be used in patients with heart failure and diabetes.

15.3.5.5 Thiazolidinedione drugs (TZDs)

RCTs have demonstrated that TZDs are associated with increased rates of HF hospitalization in patients without HF at baseline.

Recommendations

- TZDs are not recommended in patients with established HF. Caution should be exercised when starting TZDs in patients with risk of developing HF.

15.3.5.6 GLP-1 Receptor Agonists

It may reduce the risk of major adverse cardiovascular events and mortality in the general population of patients with DM.

But it has had no impact on the risk of HF hospitalization. In patients with established HFrEF and recent decompensation, GLP-1 receptor agonists should be used with caution. There is no data to guide their use in HFpEF.

Recommendations

- GLP-1 Receptor Agonists are safe to use but not beneficial in preventing HF in patients at risk for HF.

15.3.5.7 Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors)

There is no evidence that DPP-4 inhibitors provide cardiovascular benefit.

In patients with DM at high cardiovascular risk, Saxagliptin and Alogliptin could increase the risk of hospitalization for HF.

With the available data, the risk-benefit balance for most DPP-4 inhibitors does not justify their use in patients with established HF or those at high risk for HF.

Recommendations

- When glycemic control cannot be achieved with metformin and SGLT2 inhibitors, or when those are contraindicated, cardiovascular neutral DPP4 inhibitors (Sitagliptin and linagliptin) can be used in patients with heart failure and diabetes.

15.4 Diabetes and Kidney

15.4.1 Diabetic Nephropathy

Diabetes mellitus is the leading cause of chronic kidney disease and end stage kidney disease worldwide. Various forms of renal diseases can manifest in diabetes including glomerular lesions and tubulointerstitial diseases.

Diabetic Kidney Disease (DKD) is a clinical diagnosis based on persistent albuminuria and/or decreased estimated GFR (<60ml/min/1.73m²) in a patient with diabetes. Kidney biopsy is rarely performed to confirm the diagnosis. Diabetic nephropathy is a specific pathological phenotype, which is characterized by Glomerular basement membrane thickening, endothelial damage, mesangial expansion, and nodules (Kimmelstiel-Wilson nodules), podocyte injury and glomerulosclerosis.

T1DM for five years or more, and/or presence of diabetic retinopathy are highly predictive of DKD. In T2DM, DKD can even be present at the time of diagnosis (presence of diabetic retinopathy is highly predictive of DKD).

Kidney biopsy is considered in diabetics when alternative diagnosis is likely.

Example-

- Albuminuria >300mg/g within five years of onset of T1DM
- Albuminuria (>300mg/g) without diabetic retinopathy
- Active sediments in urine
- Acute increase of proteinuria
- Rapid decline of GFR

15.4.2 Screening and evaluation of DKD

15.4.2.1 Albuminuria quantification can be done with either urine albumin to creatinine ratio or 24-hour urine albumin excretion. We suggest using a second void urine sample in the morning for spot assessment of albuminuria.

- Albuminuria is graded according to the degree of urine albumin excretion.
- Normal to mildly increased albuminuria – Albumin excretion less than 30mg/g or mg/day.
- Moderately increased albuminuria – Previously termed microalbuminuria. Measured urine albumin excretion 30-300mg/g or mg/day.
- Severely increased albuminuria- Previously called macroalbuminuria. Measured urine albumin excretion more than 300mg/g or mg/day.

Table 15. 3: Albumin quantification

Category	Measured Urine Albumin	Albumin/Creatinine Ratio	Grading
A1	<30mg/g or mg/day	<3 mg/mmol	Normal (mild)
A2	30-300mg/g or mg/day	3-30mg/mmol	Microalbuminuria (Moderate)
A3	>300mg/g or mg/day	>30mg/mmol	Macroalbuminuria (Severe)

Magnitude of albuminuria positively correlates with rate of progression to end stage kidney disease (ESKD) as well as risk of CVD. Microalbuminuria is an independent risk factor for CVD and it approximately doubles the risk of CVD and death due to CVD.

In a random urine specimen, Urine protein: creatinine ratio (UPCR) can be used to roughly approximate 24-hour excretion rates. The normal UPCR is < 0.42. UPCR rather than ACR should be requested in pregnancy and where non-albumin proteinuria is suspected.

15.4.3 Management of DKD

15.4.3.1 Glycemic control

Optimizing glycaemic control may slow down the rate of decline in renal function.

It is recommended to maintain an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis.

15.4.3.1.1 More intensive glycemic control reduces the development of microvascular complications but increases risk of severe hypoglycaemia and all-cause mortality including CVD.

15.4.3.1.2 Therefore, age, body weight, duration of diabetes and severity of CKD and other comorbidities should be considered when determining glycemic targets for individual patients.

15.4.3.1.3 It is recommended use HbA1c to monitor glycemic control in patients with diabetes (T1DM and T2DM) and CKD.

Accuracy of HbA1c declines with advanced CKD (G4-G5) and dialysis treatment. It is suggested to use FPG/PPPG to monitor the glycemic control in patients with advanced CKD.

15.4.3.1.4 Glycated albumin and fructosamine have been proposed as alternative biomarkers for monitoring of long-term glycemic control, but these markers reflect glycemic control of brief time periods due to their shorter survival in blood. Further these markers are biased with hypoalbuminemia and malnutrition.



15.4 : Individualised HbA1C Targets

15.4.3.1.5 Self-monitoring of blood glucose (SMBG) or Continuous glucose monitoring (CGM) are preferred when antihyperglycaemic therapies associated with high risk of hypoglycaemia is evident.

15.4.3.1.6 In conditions where reliability of measured HbA1c is low (advanced CKD and dialysis), glucose management indicator (GMI) derived from continuous glucose monitoring (CGM) can be used (if available).

15.4.3.2 Oral Hypoglycaemic drugs (OHD)

Metformin

Glycemic management for patients with T2DM and CKD should include lifestyle therapy, first-line treatment with metformin and a SGLT-2 inhibitor, and an additional drug therapy as needed for glycemic control.

15.4.3.2.1 It is recommended to start metformin as the first-line treatment for hyperglycemia in patients with diabetes, CKD and eGFR >30.

15.4.3.2.2 Metformin is effective in achieving glycemic targets in T2DM in patients with CKD due to low risk of hypoglycaemia, further it has beneficial effects against CV events.

15.4.3.2.3 Normal renal functions or eGFR >60 does not need renal dose adjustment for Metformin. Patients with eGFR 59-45 can continue the same metformin doses as normal renal functions and monitor their renal functions more frequently at every 3-6-month intervals.

Maximum dose of metformin should be reduced to 1000mg per day when eGFR reaches 44-30 ml/min/1.73m² and should be discontinued when GFR reaches <30ml/min/1.73m².

For metformin naïve patients, it can be initiated at half the dose and titrate upwards to half of maximum recommended dose. Renal functions to be monitored 3 monthly and metformin should be discontinued if eGFR<30.

15.4.3.2.4 Monitor for vitamin B12 deficiency when metformin is continued for more than 4 years.

Table 15. 4: Use of Metformin in patients with CKD

eGFR ml/min/1.73m ²	>60	45-59	30-44
Starting dose (mg)	<ul style="list-style-type: none">➢ Immediate release➢ 500 or 850 once daily➢ Titrate upwards by 500 or 850 weekly to maximum dose (2g/day) as required➢ Extended release➢ If GI side effects from immediate release➢ 500 daily and titrate up weekly to maximum dose (2g/day) as required		Initiate at half dose and titrate up to reach half of maximum recommended dose
RFT monitoring	Annually	Every 3 to 6 months	Every 3 to 6 months

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

15.4.3.2.5 It is recommended to use SGLT2i to treat patients with T2DM, CKD, and an eGFR \geq 30.

15.4.3.2.6 SGLT2i confer renoprotective (improve albuminuria, reduce progression to severe albuminuria and worsening of CKD) and cardioprotective effects in T2DM and CKD.

15.4.3.2.7 After assessment of patients' overall risk factors, it is recommended to add a SGLT2i to other antihyperglycemic medications for patients whose glycemic targets are not currently met or who are meeting glycemic targets but safely attain a lower target.

Risk of hypoglycaemia is low with SGLT2i monotherapy but increases with concomitant use of sulfonylureas or insulin. It may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of a SGLT2i.

15.4.3.2.8 SGLT2i can cause euglycemic diabetic ketoacidosis in patients with T2DM. Therefore, it is reasonable to withhold SGLT2i during critical illness, surgery and prolonged fasting.

15.4.3.2.9 When initiating SGLT2i correct volume depletion and low blood pressure particularly when the patient is on diuretics. Before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

15.4.3.2.10 It is recommended to monitor renal functions (eGFR) after commencement of SGLT2i. It may be associated with reversible decline in eGFR, which does not warrant discontinuation.

Table 15. 5:SLGT2i dose adjustments according to level of kidney function

SGLT2 Inhibitor	Dose	eGFR eligible for inclusion in pivotal randomized trials
Dapagliflozin	5-10 mg once daily	No dose adjustment if eGFR \geq 45 ml/min/1.73m ² Not recommended with eGFR<45 ml/min/1.73m ² Contraindicated with eGFR \geq 45 ml/min/1.73m ²
Empagliflozin	10-25 mg once daily	No dose adjustment if eGFR \geq 45 ml/min/1.73m ² Avoid use, discontinue with eGFR persistently <45 ml/min/1.73m ²
Canagliflozin	100-300 mg once daily	No dose adjustment if eGFR>60 ml/min/1.73m ² 100 mg daily if eGFR 30-59 ml/min/1.73m ² Avoid initiation with eGFR<30 ml/min/1.73m ² Discontinue on Dialysis

15.4.3.2.11 Once SGLT2i are initiated, they can be continued even if eGFR falls below 30ml/min per 1.73m² unless RRT is commenced or not tolerated.

15.4.3.2.12 The use of SGLT2i in renal transplant recipients and its risk of infections on background immunosuppression have not been adequately studied.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

15.4.3.2.13 GLP-1 RA is recommended in T2DM patients with CKD where glycemic targets with metformin and SGLT2i are not achieved.

15.4.3.2.14 Long acting GLP-1 RA confers renal and cardiovascular benefits.

15.4.3.2.15 It is suggested to start with a low dose of GLP-1 RA and increase gradually to minimize the GI side effects. GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.

15.4.3.2.16 GLP-1 RA monotherapy does not lead to hypoglycaemia generally but can be increased with concurrent sulfonylureas or insulin. The dose of sulfonylurea and/or insulin may need to be reduced.

Table15. 6: GLP-1RA dose adjustments according to level of kidney function

GLP1-RA	Dose	CKD Adjustment
Dulaglutide	0.75mg and 1.5mg daily	No dose adjustment Use with eGFR >15ml/min/1.73m ²
Exenatide	10 µg twice daily	Use with CrCl >30ml/min
Exenatide extended release	2mg once weekly	Use with CrCl >30ml/min
Liraglutide	0.6mg, 1.2mg and 1.8mg daily	No dose adjustment Limited data for severe CKD
Semaglutide (injection)	0.5mg and 1mg daily	No dose adjustment Limited data for severe CKD
Semaglutide (Oral)	3mg, 7mg and 14mg daily	No dose adjustment Limited data for severe CKD

15.4.3.2.17 Other hypoglycaemic agents can be used as indicated in the table 15.7.

Table 15. 7: The use of other hypoglycaemic agents according to level of kidney function

Class	Drug	CKD stage	Dialysis	Complications
Sulphonylureas	Tolbutamide	Caution in stage 3-5	Avoid	Hypoglycaemia
	Glibenclamide	Avoid in stage 3-5	Avoid	Hypoglycaemia
	Glipizide	No dose adjustment	No dose adjustment	
	Gliclazide	No dose adjustment	No dose adjustment	
	Glimipiride	Low dose (1mg /day) in stage 3-5	Avoid	
Alpha glucosidase inhibitors	Acarbose	Avoid in stage 3-5	Avoid	Hepatic
Thiazolidinediones (TZD)	Pioglitazone	No dose adjustment	No dose adjustment	Fluid retention Risk of fractures
DPP-4 inhibitors	Sitagliptin	Reduce dose by 25% when eGFR 30-50. Reduce dose by 50% when eGFR <30.	Reduce dose by 50%	Hypoglycaemia
	Vildagliptin	Reduce dose to 50mg/day when eGFR <30.	Reduce dose to 50mg/day, but use with caution	Hypoglycaemia
	Linagliptin	No dose adjustment	No dose adjustment	

15.4.3.2.18 All types of insulin can be used in CKD, but type and dose must be individualized.

Renal clearance of insulin will be reduced as eGFR falls and a dose reduction may be necessary.

Due to the risk of hypoglycaemia shorter acting insulins may be preferred as eGFR falls. Combining oral hypoglycaemic agents with insulin may increase the risk of hypoglycaemia.

15.4.3.3 Statins

15.4.3.3.1 It is recommended to start a statin in early DKD as it reduces mortality and CV events, but not in patients who are already on dialysis as there is no benefit.

15.4.3.3.2 It is not recommended to initiate a statin or statin/ ezetimibe treatment for patients on dialysis. But those drugs should not necessarily be discontinued once dialysis is initiated.

15.4.3.4 Blood pressure control

It is recommended to use standardized office BP in preference to routine office BP for the diagnosis and management of high BP in adults. The DASH type diet or use of salt substitutes which are rich in potassium may not be appropriate for patients with advanced CKD or potential for hyperkalemia.

It is suggested that adults with CKD and high BP be treated with a target systolic BP of less than 120 mmHg.

Renin-angiotensin system (RAS) blockade

15.4.3.4.1 It is recommended to initiate treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin ii receptor blocker (ARB) in patients with diabetes, hypertension, and albuminuria, and to titrate these medications to the highest approved dose which is tolerated.

15.4.3.4.2 ACEi or ARB may be considered even in patients with diabetes, proteinuria and normal blood pressure.

15.4.3.4.3 Moderately or severely elevated proteinuria is related with increased renal and cardiovascular risk compared to normal albumin excretion.

15.4.3.4.4 RAAS blockade shows CVD and renal protection (albuminuria progression, doubling of serum creatinine and CVD and all-cause mortality) independent of blood pressure lowering effect and is preferred in patients with DKD compared to other antihypertensives.

15.4.3.4.5 No superior efficacy of ACEi over ARB or vice versa. Choice between two drugs depends on the patient's preference, cost, availability, and side effect profile.

15.4.3.4.6 ACEi can cause ACEi induced cough in about 10% of patients. We suggest switching to an ARB.

15.4.3.4.7 ACEi and ARB are potent medications to cause hypotension, hyperkalemia and increase in serum creatinine.

15.4.3.4.8 It is suggested to monitor blood pressure, serum creatinine and serum potassium within two to four weeks of initiation of ACEi and ARB as well as in increment of dosage.

15.4.3.4.9 It is suggested to continue with ACEi and ARB unless serum creatinine rises by more than 30% within four weeks of initiation or increase in dosage.

15.4.3.4.10 It is suggested to manage hyperkalemia associated with RAAS blockade with measures to reduce serum potassium rather than decreasing or stopping them (low potassium diet, avoid concurrent medications causing hyperkalemia e.g., NSAIDS, avoid

constipation, initiate diuretics to enhance renal excretion of potassium, sodium bicarbonate therapy and gastrointestinal cation exchangers). If hyperkalemia is refractory to medical management or symptomatic hypotension, consider reduction or discontinuation of drug doses.

15.4.3.4.11 It is recommended to use only one RAAS blockade agent at a time. Combination of RAAS blocking agents have not been shown to have any success and could even be harmful due to increased risk of hyperkalemia and AKI.

Combination of an ACEi or ARB with a direct renin inhibitor is potentially harmful.

15.4.3.4.12 It is suggested to use mineralocorticoid receptor antagonists for management of refractory hypertension if eGFR is more than 45 when there is no history of high serum potassium. But those should not be used in patients with low eGFR ($<45 \text{ ml/min/1.73m}^2$) and high risk of hyperkalemia.

15.4.3.4.13 It is suggested to advice on contraception in women who are in childbearing age and receiving ACEi or ARB. Women who become pregnant while on ACEi and ARB, should be stopped immediately and monitored for fetal and neonatal complications.

15.4.3.4.14 Treat the adult kidney transplant recipients with high BP to a target BP that is $<130 \text{ mmHg}$ systolic and $<80\text{mmHg}$ diastolic. It is recommended to use a dihydropiridine calcium channel blocker or an ARB as the first line antihypertensive agents.

15.4.4. Nutrition

Shared decision making is a cornerstone of patient-centered nutrition management in patients with diabetes and CKD. Obesity is associated with a more rapid decline of kidney function. Therefore, weight loss may be appropriate in early CKD. However, in advanced CKD, malnutrition is common and is multifactorial.

15.4.4.1 In diabetes and CKD, nutrition management should be tailored to individual patients. It is suggested to maintain total protein intake of 0.8g protein/kg/day for adults with diabetes and non-dialysis advanced CKD ($e\text{GFR}<30 \text{ ml/min/1.73m}^2$). For patients on hemodialysis or peritoneal dialysis, daily protein requirement would be 1-1.2g protein/kg/day.

15.4.4.2 Patients with diabetes and CKD should be encouraged to have a diet rich in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, and nuts. Processed meats, refined carbohydrates and sweetened beverages should be discouraged.

15.4.4.3 Sodium restriction may enhance the effect of RAAS blockade (antihypertensive effect and anti-albuminuric effect).

It is suggested to restrict the sodium intake to $<2\text{g}$ of sodium per day (or $<90 \text{ mmol}$ of sodium per day, or $<5\text{g}$ sodium chloride per day) in patients with diabetes and CKD.

15.4.5 Lifestyle modifications-

15.4.5.1 Smoking

It is recommended to advise patients with diabetes and CKD to quit smoking and to avoid all other tobacco products. Physicians should counsel patients with diabetes and CKD to reduce secondhand smoke exposure.

15.4.5.2 Strategies to stop smoking include behavioral interventions as well as medications (nicotine replacement therapy-patch, gum, lozenges, inhalers and nasal sprays or bupropion and varenicline).

15.4.5.3 Physical activity

It is recommended to engage with moderate intensity physical activity for cumulative duration of 150 minutes or more per week or to a level compatible with their cardiovascular and physical tolerance.

15.4.5.4 Obesity

Sedentary lifestyles should be discouraged. Physicians should advise/encourage patients with obesity, diabetes, and CKD to lose weight, particularly when eGFR \geq 30 ml/min/1.73m².

15.4.5.5 It is suggested to provide integrated care when managing a patient with diabetes and CKD by a multidisciplinary team consisting of physicians, trained nurses, dieticians, pharmacists, health care assistants, community workers, peer supporters and policymakers.

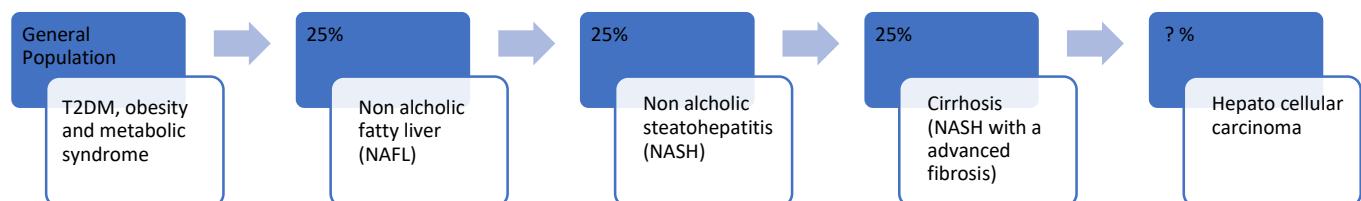
15.5 Diabetes and liver

15.5.1 Introduction

- Patients with diabetes can have number of liver dysfunctions but nonalcoholic fatty liver disease (NAFLD) is one of the commonest. The relationship between NAFLD and T2DM is bidirectional. Diabetes promotes the progression of nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH) and increases the risk of cirrhosis and hepatocellular carcinoma (HCC). On the other hand, NAFLD is associated with an increased risk of developing T2DM.
- The liver is the major site of drug metabolism including many anti-diabetic drugs. In presence of liver dysfunction anti-diabetic drugs have altered pharmacodynamics and pharmacokinetics properties and can result in many unwanted side effects including hypoglycaemia or even lactic acidosis.

15.5.2 Nonalcoholic fatty liver disease (NAFLD)

- The diagnosis of NAFLD requires there is evidence of hepatic steatosis (>5% steatosis), either by imaging or histology, and lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long term use of steatogenic medications or monogenic hereditary disorders.
- Prevalence of NAFLD in Diabetes is estimated at 34-74% and in diabetes with morbid obesity, it reaches almost 100%.
- In Sri Lanka, the prevalence of ultrasonically detected NAFLD among urban adults is 32.6% and among rural adults is 18%.
- Natural history of NAFLD can range from simple steatosis, hepatic inflammation to cirrhosis and even hepatocellular carcinoma. Multiple factors influence the progression of disease.



15.5 : Natural History of NAFLD

When to suspect NAFLD

- We recommend screening for NAFLD in T2DM patients having obesity or features of metabolic syndrome.
- We suggest patients with T2DM having elevated liver enzymes or fatty liver on ultrasound scan should be evaluated for NAFLD.
- Routine population screening for NAFLD is not recommended due to lack of evidence of benefit.

15.5.2.4 Noninvasive investigations to evaluate of NAFLD

Ultrasound scan abdomen is recommended as an initial investigation for screening patients suspected of NAFLD.

Liver Magnetic Resonance imaging (MRI), MR spectroscopy, MR elastography, Fibro Scan (Vibration controlled transient elastography – VCTE) are some non-invasive investigations that can also be used to evaluate NAFLD.

Serum based score [NAFLD fibrosis Score (NFS) and FIB4 score] calculators are freely available on the web, easy to use and helpful in risk stratification of NAFLD patients but not validated in Sri Lankan population.

In considering diagnosis of NAFLD secondary causes of hepatic fat accumulation need to be excluded including significant alcohol intake.

15.5.2.5 Liver biopsy in NAFLD

Liver biopsy remains the gold standard for diagnosing and staging the liver histology in patients with NAFLD.

15.5.2.6 Management of patient with T2DM and NAFLD

The management of NAFLD aims at preventing the progression of liver disease by managing metabolic derangements such as obesity, hyperlipidemia, insulin resistance, and T2DM.

15.5.2.7 Lifestyle modification

Lifestyle modification consisting of diet, exercise and weight loss has a very important part in management of patients with NAFLD.

15.5.2.7.1 Diet

We recommend low calorie Mediterranean diet.

Calorie-restricted diet over the long term is associated with mobilization of liver fat and improvement in cardiovascular risk. Clinical studies have shown decreasing caloric intake by at least 30% or by approximately 750-1000kcal/day result in improvement of insulin resistance and hepatic steatosis.

(Please refer – Dietary management 16.2)

15.5.2.7.2 Exercise

We recommend moderate to vigorous intensity aerobic exercise at least 150 minutes per week for patients with T2DM and NAFLD.

Exercise had clearly demonstrated to improve hepatic steatosis. Data suggest patients who maintain moderate physical activity more than 150minutes per week have more pronounce decrease in aminotransferases, independent of weight loss.

(Please refer – Exercise in diabetes 16.1)

15.5.2.7.3 Weight loss

A greater weight loss (>10%) is recommended to improve the histopathological features of NASH, including fibrosis.

- **A combination of a calorie-restricted diet and moderate intensity exercise is likely to provide the best likelihood of sustained weight loss over time.**

- 5-7% weight loss will result in resolution of steatosis.
- 7-10% weight loss will result in resolution of steatohepatitis.
- >10% weight loss will result in regression of fibrosis.

15.5.2.8 Pharmacological treatments in patients with T2DM and NAFLD

There are no approved pharmacological agents for treatment of NAFLD, but a few already available medications for treatment of T2DM have shown to be effective in NAFLD. T2DM patients on thiazolidinediones (pioglitazone), SGLP2 inhibitors and GLP 1receptor agonist (liraglutide) have shown improvement in NAFLD.

15.5.2.8.1 We suggest all patients with T2DM and NAFLD to be assessed for CVD risk factors. CVD is the commonest cause of death among patients with NAFLD.

15.5.2.8.2 We suggest patients with T2DM and NAFLD to be assessed for liver related complications and extra hepatic malignancies.

Liver related mortality and extra hepatic malignancies are second and third commonest causes of death in patients with NAFLD.

Diabetes is more common among Hepatitis C infected patients.

Data showing patients with Hepatitis C are more likely to develop diabetes (21%) than patients with hepatitis B (10%).

15.5.3. Prescribing in chronic liver disease

15.5.3.1 Insulin

Insulin therapy remains the treatment of choice for patients with T2DM and advanced cirrhosis (Child-Pugh class C).

Short-acting insulin is preferred due to less risk of hypoglycaemia

15.5.3.2 Biguanides (Metformin)

Metformin therapy is safe in T2DM patients with compensated cirrhosis and may benefit them by prolonging survival time.

15.5.3.2.1 Patients with T2DM and compensated cirrhosis, metformin use was associated with lower risk of overall mortality, liver transplant and HCC. Metformin an insulin sensitizer but does not significantly impact resolution of NASH or fibrosis and is considered neutral with regard to NAFLD.

15.5.3.2.2 It is recommended to avoid metformin in patients with severe liver disease (Child-Pugh class C) or in binge drinkers due to incidence of lactic acidosis.

Patients with multiple co-morbidities, such as renal, liver and cardiac disease, particularly in acute deterioration, when treated with metformin appear to be at higher risk of lactic acidosis.

15.5.5.4 Thiazolidinediones- Pioglitazone

15.5.5.4.1 Pioglitazone is recommended for patients with T2DM and NAFLD provided there are no contraindications.

Pioglitazone improves liver histology in patients with and without T2DM with biopsy proven NASH. Pioglitazone treatment is associated with edema and weight gains

15.5.5.5 GLP 1 receptor agonists

Liraglutide is recommended in T2DM patients with NAFLD

Liraglutide not only improved T2DM but also resulted in improvement of liver inflammation, alteration of liver fibrosis and reduction of body weight

15.5.5.6 SGLT2 Inhibitors

SGLT2 inhibitors may benefit T2DM patients with NAFLD

A recent randomized control trial had shown significant reduction in hepatic steatosis in patients with T2DM and NAFLD treated with empagliflozin.

15.5.5.7 Statins

15.5.5.7.1 Statins can be safely used to treat dyslipidemia in patients with NAFLD and NASH, NASH cirrhosis.

CVD is the commonest cause of death in patients with NAFLD.

15.5.5.7.2 Statins should not be used in patients with decompensated cirrhosis.

15.5.5.8 Sulfonylureas

Short half-life sulfonylureas such are preferred over long acting sulfonylureas in CLD patients due to risk of hypoglycaemia.

15.5.5.9 Alpha glucosidase inhibitors

Patients with liver cirrhosis may benefit from alpha glucosidase inhibitors.

Alpha glucosidase inhibitors improve post prandial hyperglycemia in patients with compensated cirrhosis. It had been shown to improve grade 1/2 hepatic-encephalopathy in patients with cirrhosis and T2DM.

Alpha glucosidase inhibitors should be avoided in advanced liver disease (Child-Pugh class C).

15.6 - Glycemic management in critical care set up

15.6.1 Introduction - Reproduce the endocrine pancreas in critically ill

Hyperglycemia is a common problem in critically ill patients, caused by complex interactions associated with inflammation due to overwhelming immune response, counter-regulatory responses along with impaired glucose tolerance. Further, hyperglycemia is exacerbated by unsuppressed endogenous glucose production, some medications such as steroids and catecholamine, and exogenously administered nutrition. Additionally, there is suppression or loss of pancreatic insulin secretion, and insulin resistance, resulting in reduced insulin-mediated glucose uptake. Further, the glycemic variability, acute fluctuations in blood glucose levels, is also known to be much more dangerous than persistent hyperglycemia in critically ill patients.

An effective protocol for the glycemic control should provide insulin similar to a normal subject responding to hyperglycemia, resembling an artificial pancreas. The pancreas is linked to a continuous, accurate glucose "sensor" to guide insulin secretion and control. Therefore, the essential requirements for "an artificial pancreas in the ICU" include accurate high-frequency continuous glucose monitoring, continuous intravenous insulin infusion and an effective protocol that controls the intravenous insulin infusion.

15.6.2. Recommendations on glycemic targets

- It is recommended to initiate insulin therapy for the treatment of persistent hyperglycemia with a threshold of 180 mg/dL.
- Once the insulin therapy is initiated, it is recommended to achieve a glycaemic level of 140–180 mg/dL for the majority of critically ill patients.
- It is suggested to achieve tight glycemic targets, such as 110–140mg/dL, for selected patients appropriately, if this can be achieved without significant hypoglycaemia.
- In terminally ill patients and in patients with severe co-morbidities, it is suggested that higher glucose ranges might be acceptable.

It is recommended to commence insulin in patients with persistent hyperglycemia above 180 mg/dL in critically ill patients, and to maintain the glycemic range between 140-180 mg/dL. It is recommended to achieve these glycemic targets in patients with sepsis, myocardial infarctions, as well as in neuro-critical care and post-surgical ICU care.

These recommendations are based on meta-analysis including 26 studies along with Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, which demonstrated an increased rate of severe hypoglycaemia (defined as blood glucose of 40 mg/dL) and higher mortality in patients with tight versus moderate glycemic control.

15.6.3. Recommendations on anti-hyperglycemic agents

- It is suggested to consider intravenous insulin infusion as the preferred therapy and to administer the therapy based on written or computerized protocols that allow predefined adjustments in the infusion rate according to glycemic fluctuations.

- It is suggested to continue insulin therapy with basal bolus regimen for less-critically ill patients with good nutritional intake.

In the critical care setting, insulin is the preferred treatment for hyperglycemia rather than oral therapy in most instances. It is suggested that the glycemic control should be maintained with insulin due to the effectiveness, quick action, and few contraindications which would otherwise complicate the therapy.

15.6.4. Recommendations on bedside blood glucose monitoring

- It is suggested to measure blood glucose levels frequently ranging from every 30 min to every 2 h for patients receiving intravenous insulin.

Continuous glucose monitoring as point of care testing or as real time basis with sophisticated measurements provides frequent measurements of body glucose levels and supports in detecting and reducing the incidence of hypoglycaemia in the critical care setting. Real time continuous glucose monitoring is still not widely established as a recommendation since studies have shown that it did not improve glucose control beyond point of care testing. However, it has detected a greater number of hypoglycaemic events than point of care testing.

15.6.5. Recommendations on management of hypoglycaemia

- It is suggested to establish a plan for preventing and treating hypoglycaemia for each patient.
- It is suggested to document and to clinically evaluate each episode of hypoglycaemia clearly.

It is suggested to review the overall treatment regimen of the patient when the blood glucose value of 70 mg/dL is identified because such readings often predict imminent level 3 hypoglycaemia. See chapter 14.3 for the evaluation and management of hypoglycaemia.

15.6.6. Recommendations on insulin Infusion Protocols

- It is suggested to administer intravenous insulin infusion based on written or computerized protocols that allow predefined adjustments in the infusion rate according to glycemic fluctuations.

The requirement of achieving satisfactory glycemic control in the ICU while avoiding significant hypoglycaemia and glycemic variability has resulted in numerous protocols and algorithms for intravenous insulin delivery. The algorithms are usually implemented as written instructions, with adjustments carried out by ICU nurses whenever a new glucose value is available. The most algorithms have been developed and tested based on the experiences of nurses and doctors at different institutions. Well established examples include the Portland protocol [P] (appendix 1) designed for a surgical cardiac ICU, an algorithm developed at the University of Washington [UW] (appendix 2) used for any hyperglycemic ICU patient, and another algorithm developed at Yale University [Y] (appendix 3) designed for a medical ICU. UW protocol is the one which is commonly adopted in Sri Lankan ICUs. However, at present, no single protocol or algorithm has been established as the most effective for maintaining tight glycemic control compared to each other.

UW algorithm which uses multiple sliding scales increases insulin delivery in response to hyperglycemia by increasing the algorithm's sensitivity to glucose. P protocol increases insulin delivery by incrementing the rate directly. The Y protocol utilizes both mechanisms.

Algorithms that incrementally increases insulin in response to glucose without changing the sensitivity (P protocol) is known to bring patients to target glucose with the lowest risk of hypoglycaemia but will take longer to achieve target levels in patients who are insulin resistant. Algorithms that increment insulin by changing the sensitivity (UW and Y protocols) are known to adapt to the insulin resistance and control the glycaemia quickly. However, if the sensitivity changes with time unknowingly, these algorithms have a higher risk of hypoglycaemia.

15.6.7. Recommendations on parenteral/continuous enteral feeding in the ICU

- It is suggested to adjust insulin therapy considering basal, prandial, and correctional components for patients who are receiving enteral or parenteral feedings when insulin is required.

Hyperglycemia is a frequent complication of enteral and parenteral nutrition in ICU patients. Parenteral nutrition induced hyperglycemia is a serious complication which results in higher rates of longer intensive care unit stays, longer hospital stays, and higher mortality rates when compared with patients without hyperglycemia.

Managing hyperglycemia in these patients should include optimization of carbohydrate content and administration of preferably intravenous or subcutaneous insulin therapy. The administration of continuous insulin infusion and insulin addition to nutrition bag are efficient approaches to control hyperglycemia during parenteral nutrition.

A suggested protocol for the administration of insulin for such patients is given in the Annexure 4.

15.6.8. Recommendations on transitioning Intravenous to subcutaneous Insulin

- It is suggested to apply a transition protocol when discontinuing intravenous insulin, which is known to be associated with less morbidity and lower costs of care.

It is recognized that use of a standardized protocol for the transition from intravenous to subcutaneous insulin in ICU patients, would improve the effectiveness of glycemic management while maintaining the safety avoiding rebound hyperglycemia or hypoglycaemia when regular oral feeding is resumed. There are multiple protocols which have been validated. Such a validated protocol is given in the appendix 5.

15.7 Diabetes management during acute illness in hospital setting

15.7.1 Introduction

Diabetes increases the risk of hospitalization of a person due to several reasons including cardiovascular (CVD) disease, nephropathy, infections, cancer and lower extremity amputations.

The association between hyperglycemia in hospitalized patients (with or without diabetes) and increased risk for complications and mortality is well established. Hypoglycaemia is equally important and associated with many complications as well. Avoiding both hyper and hypoglycaemia and optimizing glycemic control among acutely ill patients with diabetes during hospital stay will result in less complications and achieving a favorable clinical outcome.

15.7.2 Identifying patients with diabetes and hyperglycemia, on admission to hospital.

15.7.2.1 It is suggested to identify all patients with a history of diabetes, on admission to hospital and document the type of diabetes, current medications, and any preexisting complications.

15.7.2.2 It is suggested that all acutely ill patients with no prior history of diabetes should be screened for diabetes and hyperglycemia.

Hyperglycemia in hospitalized patients is defined as blood glucose level of >140 mg/dl (7.8 mmol/L).

Stress induced hyperglycemia is common in hospitalized patients, even among those without a previous history of diabetes, and is associated with increased in hospital complications, longer length of stay and mortality. Acute illness causes number of physiological changes (e.g., increase in circulatory stress hormones) or therapeutic choices (e.g., glucocorticoid use) that can exacerbate Hyperglycemia.

15.7.3 Evaluating patient with hyperglycemia

15.7.3.1 It is recommended to check HbA1c in all hospitalized patients with newly diagnosed hyperglycemia.

An admission HbA1c $> 6.5\%$ (48mmol/l) suggest that onset of diabetes predate hospital admission, HbA1c 5.7 - 6.5% would suggest prediabetes, whereas HbA1c < 5.7 (38.8mmol/l) means patient is having hyperglycemia due to acute illness.

15.7.3.2 It is suggested to monitor capillary plasma glucose (CPG) in hospitalized patients with CPG >140 mg/dl or HbA1c $>6.5\%$.

15.7.4 Glycemic targets for acutely ill hospitalized patients

15.7.4.1. It is recommended a pre-meal plasma glucose target of <140 mg/dl (7.8mmol/L) and a random plasma glucose target of <180 mg/dl (10mmolL) for hospitalized patients with non-critical illness.

15.7.4.2 It is suggested to modify the glycemic targets according to clinical status of the patient.

- More stringent blood sugar goal of 110-140mg/dl (6.1-7.8mmol/L), may be appropriate for selected patients if they can be achieved without significant hypoglycaemia.
- A less stringent blood sugar level of >180 mg/dl (10mmol/L) may be acceptable in terminally ill patients or patients with severe co-morbidities in hospital.

15.7.4.3 Provided the patient's medical condition, dietary intake and glycemic control are stable, they could be maintained on their pre-hospital oral hypoglycaemic or insulin regimen.

15.7.4.4 It is suggested to adjust insulin doses considering the differences in meals and activity levels while in the hospital.

15.7.5 Insulin therapy in hospitalized acutely ill patient

15.7.5.1. It is recommended to initiate insulin therapy when blood glucose level is persistently above 180mg/dl (10mmol/L) in non-critically ill hospitalized patients.

15.7.5.2 Insulin is the preferred treatment for hyperglycemia in hospitalized patients with diabetes. Patients with type 1 diabetes must be maintained on insulin therapy at all times to prevent DKA.

In a critically ill patient, continuous intravenous insulin infusion is the most effective method for achieving glycemic targets.

When transitioning from intravenous to subcutaneous insulin, patients should receive 50% of daily infusion dose as basal insulin 2-4 hours before the infusion is stopped.

(Please refer chapter 14 – Management of Diabetic Emergencies)

15.7.6. In non-critically ill hospitalized patients with diabetes or stress hyperglycemia. (Grade A, Level 1) (2, 4, 5, 10)

It is recommended that subcutaneous insulin regimen should consists of basal, bolus (prandial) and correction (supplemental) insulin components in non-critically ill hospitalized patients with diabetes or stress hyperglycemia

Example of a basal-bolus-correction insulin regimen for the management of non-critically ill patients with T2DM.

Discontinue both oral and non-insulin injectable diabetes medications when starting insulin.

A. Basal insulin order

Calculate the total daily dose of insulin as follows:

- 0.2 – 0.3 U/kg of body weight in a patient >70 years and /or eGFR <60ml/min.
- 0.4 U/kg of body weight for a patient not meeting the above criteria and has a blood glucose concentration of 140-200mg/dl
- 0.5 U/kg of body weight for a patient not meeting the above criteria and has a blood glucose concentration 201-400mg/dl
- 50% of calculated total daily dose of insulin is given as basal insulin
- Give basal insulin once (glargine/detemir/degludec) or twice (detemir/NPH) daily at the same time each day

B. Bolus insulin order

- 50% of the calculated total daily dose of insulin is given as bolus insulin.
- Give rapid/short acting (prandial) insulin in three equally divided doses before each meal.
- Hold prandial insulin if patient is not able to eat.

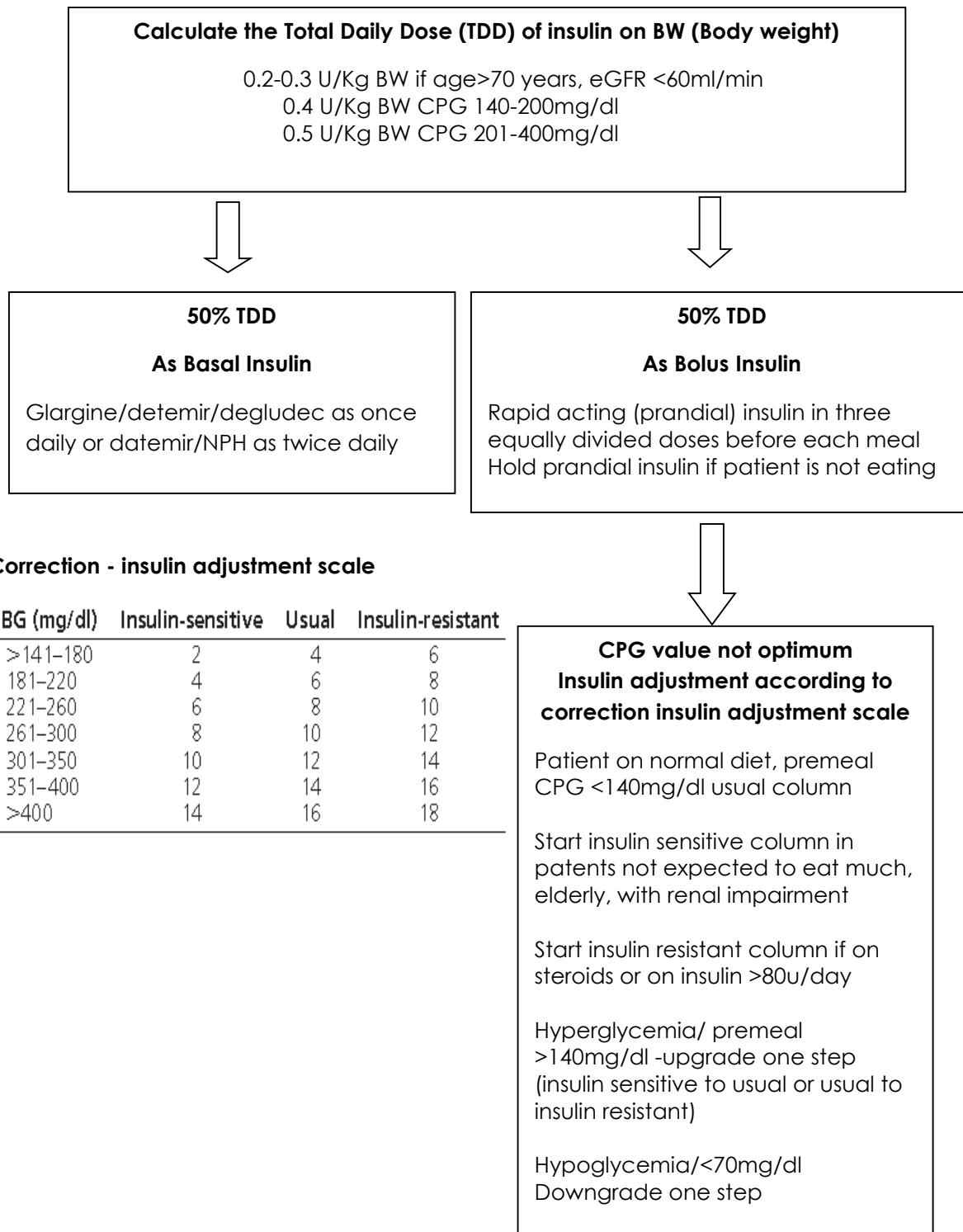
C. Correction insulin order

- Adjust insulin dose according to the results of bedside CPG measurements and referring to correction insulin scale (D).
- The numbers in each column of correction insulin scale (D) indicate the number of units of regular or rapid-acting analog insulin per dose.
- If the patient is not able to eat, give regular insulin every 6h (6-12-6-12) or rapid acting insulin every 4-6h following the sensitive column – **section D** below
- Start at insulin-sensitive column in patients who are not eating, elderly patients and those with impaired renal function.
- Start at insulin-usual column if the patient is able and expected to eat all or most of his/her meals.
- Start at insulin-resistant column in patients receiving corticosteroids and those treated with more than 80 U/d before admission.
- If fasting and premeal plasma glucose are persistently above 140mg/dl in absence of hypoglycaemia, increase insulin scale of insulin from the insulin-sensitive to the usual or from the usual to the insulin-resistant column.
- If a patient develops hypoglycaemia blood glucose <70mg/dl, decrease the regular or rapid acting insulin from the insulin-resistant to the usual or from usual to insulin-sensitive column.
- Correction (supplemental) insulin dose is to be added to the scheduled insulin dose. Give half of supplemental insulin dose at bedtime.

D. Correction (Supplemental) insulin scale

BG (mg/dl)	Insulin-sensitive	Usual	Insulin-resistant
>141–180	2	4	6
181–220	4	6	8
221–260	6	8	10
261–300	8	10	12
301–350	10	12	14
351–400	12	14	16
>400	14	16	18

Example of a basal bolus insulin regimen for the management of non-critically ill patients with T2DM



15.6: Example of basal bolus insulin regimen for the management of non-critically ill patients with T2DM

15.7.7. It is recommended not to use sliding scale insulin regimen for hospitalized patients.

It is suggested that not to use premixed insulin regimens routinely for in hospital use due to risk of increased hypoglycaemia.

Patients on enteral or parenteral feeding, who require insulin, the regimen should include coverage of basal, prandial and correctional needs.

15.7.8 Recommendations for bedside plasma glucose monitoring

- The frequency and timing of bedside CPG monitoring should be individualized to each hospitalized patient.
 - Before meals and at bedtime in patients who are eating
 - Every 4-6h in patient who are not eating or receiving continuous enteral feeding
 - Every 1-2h for patients on continuous intravenous insulin or those who are critically ill.
- Any CPG result that does not correlate with the patient's clinical status should be confirmed with a serum plasma glucose measurement.
- CPG readings are subjected to artifact due to perfusion, edema, erythrocytosis and several commonly used medications.

15.7.9 Avoiding Hypoglycaemia

15.7.9.1 It is suggested to implement a hypoglycaemia management plan in each hospital that includes avoidance of hypoglycaemia, recognition and initial treatment plan.

15.7.9.2. It is suggested to review and change the treatment regimen as necessary when a patient's blood sugar level <70mg/dl to prevent further hypoglycaemic episodes.

In a hypoglycaemic patient the following should be checked.

- Errors in insulin dosing and/or administration.
- Improper prescribing of other glucose lowering medication
- Inappropriate management of first episode of hypoglycaemia
- Nutrition-insulin mismatch often due to unexpected interruption in nutrition
- Acute kidney injury, possibly as a result of decrease insulin clearance
- Sudden reduction in corticosteroid dose
- Reduction in oral intake and emesis.
- Inappropriate timing of short or rapid acting insulin in relation to meals.
- Reduced infusion rate in intravenous dextrose.
- Unexpected interruption of enteral or parenteral feeding.
- Altered ability of patients to report symptoms.
- Lack of hypoglycaemic awareness

15.7.10 Management of hyperglycemia in patients with steroid (Glucocorticoid) therapy.

Short acting glucocorticoid such as prednisolone reach peak plasma levels in 4-6 h but have a pharmacologic action that last throughout the day. Patients on morning steroid regimens have

disproportionate hyperglycemia during the day, but they frequently reach normal blood glucose levels overnight regardless of treatment.

15.7.10.1 It is suggested to administer an intermediate acting insulin as a prandial dose for diabetes patients on once daily steroid dose with elevated blood glucose.

15.7.10.2 When long-acting glucocorticoids or high doses of glucocorticoids are used, it is suggested to use an insulin regimen consisting of basal, bolus (prandial) and correction (supplemental) insulin components. Sometimes extraordinary high doses of insulin may be needed to control blood glucose.

Whatever insulin regimen is started, dose adjustments based on anticipated change in glucocorticoid dosing and bedside CPG results need to be considered.

15.7.11 Management of diabetes in acute coronary syndrome (ACS)

It is suggested that blood sugar target of 140-180mg/dl for patients with ACS.

- o Hyperglycemia during the first 24 to 48 hours of ACS is associated with an increased early mortality, whether the patient is having diabetes or not.
- o Although some studies have shown short term intensive glycemic control immediately post MI may be beneficial, further studies have shown neither more aggressive control nor long term insulin therapy carry any additional benefit but are harmful.
- o Improved glycaemic control has been associated with better survival in ACS, but the method of glucose lowering and the target range for glucose remain indeterminate. Insulin may be more beneficial in some subgroups of ACS patients and not all.

15.7.12. Review of oral hypoglycaemic medications in acutely ill in-hospital patients

It is suggested to review the existing oral hypoglycaemic medications and doses in acutely ill in-hospital patients with diabetes.

Acutely ill patients with diabetes might have many comorbidities including heart failure, renal failure and liver failure that will need dose adjustment or withdrawal (e.g., Metformin).

15.7.13 Medical nutrition therapy in hospital

The goal of medical nutrition therapy in the hospitalized patients is to provide adequate calories to meet metabolic demands, optimize glycemic control, address personal food preferences and facilitate creation of a discharge plan.

15.7.14 Discharge from hospital

It is recommended that a structured discharge plan tailored to individual patient may reduce length of hospital stay and readmission rates and increase patient satisfaction.

Patients need to be stabilized on long term medications (including oral hypoglycaemic or regular insulin regimen) before discharge.

All medications need to be reviewed depending on patients clinical and laboratory parameters.

15.8. PERI-OPERATIVE CARE IN DIABETES

15.8.1 Pathophysiology of Surgical and Anesthetic Stress on Blood Sugar

The stress of surgery and general anesthesia cause a neuroendocrine stress response with release of counter regulatory hormones, such as epinephrine, glucagon, cortisol, and growth hormone, and inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha to the circulation.

These neurohormonal changes result in metabolic abnormalities including insulin resistance, decreased peripheral glucose utilization, impaired insulin secretion, increased lipolysis, and protein catabolism, leading to hyperglycemia and even ketosis in some cases.

In addition to the surgical stress, type of anesthesia and surgery, hypothermia, steroids, vasoconstrictors, enteral and parenteral feeding, immunosuppressives, patient factors like infection/trauma also contribute to the degree of hyperglycemia.

15.8.2 Outcome of Poor Glycemic Control in Peri-Operative Period

Diabetes affects 10–15% of the surgical population and patients with diabetes undergoing surgery have greater complication rates (infections, poor wound healing, acute kidney injury and acute coronary events), mortality rates and length of hospital stay. The risks would be there for patients who develop stress hyperglycemia as well.

Studies have shown that high pre-operative and peri-operative glucose and glycated hemoglobin (HbA1c) levels are associated with poor surgical outcomes in both elective and emergency surgeries.

15.8.3 Pre-operative Optimization Prior to Surgery

15.8.3.1 The treating doctor should arrange early pre-operative optimization of glycemic level in patients planned for elective surgeries. It should be targeted on level of glycemic control (HbA1c), assessment of risk of hypoglycaemia and hypoglycaemic awareness, assessment of diabetes related complications: renal, macrovascular, autonomic neuropathy and, optimizing them prior to surgery.

15.8.3.2 The broad goals of pre-operative glycemic management include prevention of hyperglycemia, prevention of hypoglycaemia and prevention of diabetic emergencies: DKA and HHS.

15.8.3.3 The pre-operative HbA1c target should be less than 8.5% (69 mmol/L) if it can be achieved safely to minimize peri-operative complications in elective surgery. Additionally, self-monitoring of blood glucose (SMBG) records may be helpful in assessing glycemic control.

15.8.3.4 Those who have HbA1c >8.5% are considered to be referred to the specialist team for optimization of glycemic control prior to elective surgery. The risk of going ahead with surgery when the control is suboptimal should be balanced against the urgency of surgery.

15.8.4. Hospital Admission

- 15.8.4.1** **High** risk patients should be identified (poor glycemic control/complications of diabetes) and arrangements should be made to admit the patient to an ICU or HDU in the post-operative period if required.
- 15.8.4.2** **Identify** those with high-risk feet and peripheral vascular disease. Pressure areas should be identified, and measures should be taken to prevent pressure ulcers during surgery and post - operative period. Stockings to prevent venous thrombosis should be used cautiously in those with peripheral vascular disease.
- 15.8.4.3** **Prioritize** patients with diabetes on the list. Minimize starvation time.
- 15.8.4.4** The target glucose for the pre-operative anaesthetized or sedated patient or those who are on insulin or sulphonyl urea which may cause hypoglycaemia should be 110- 180 mg/dl. (Up to 220 mg /dl is acceptable). In the awake patient on agents that do not produce hypoglycaemia, provided they have not been given insulin, a lower glucose value down to 70 mg/dl is acceptable and does not warrant rescue therapy.
- 15.8.4.5** **Closely** monitor CBG in patients who have been sedated and who are at risk of hypoglycaemia, as hypoglycaemia could be wrongly interpreted as sedation.
- 15.8.4.6** **If** the fasting period is expected to be limited to one missed meal, the patient can be managed by modification of his/her usual diabetes medication.
- 15.8.4.7** **Recommendations** for pre-operative Modification of antidiabetic therapies before surgery; day prior to admission and day of surgery is tabulated below.

Table 15.8 Perioperative adjustment of anti-diabetic therapies

	Night before procedure	Morning of the procedure
Patient taking oral diabetes medications	Take usual dose except SGLT2 inhibitors*	Hold dose
Patient taking evening or bedtime insulin		
Intermediate acting insulin (NPH)	Take usual dose	Take 50% of usual dose
Pre-mixed insulin*	Take usual dose	Take 50 % of usual dose
Long-acting insulin* Glargine/Detemir (monotherapy)	50% of usual dose	Take 50% of usual dose
Long-acting insulin Glargine/Detemir (part of BBR)	Take 70 % of usual dose	Take 70 % of usual dose
Regular or ultra-short acting insulin	Take usual dinner dose	Hold doses
Patients on non-insulin injectables	Take usual dose	Hold doses
Patients using insulin pumps	Continue basal rate. Then reduce to temporary basal rate of 70%	Reduce to temporary basal rate of 70%

SGLT2-inhibitors need to be withheld at least 2 days prior to major procedure to prevent the risk of euglycemic ketoacidosis.

*it is safe to convert pre-mixed insulin to BBR before a procedure

*Degludec due to its long half-life, if given in the night reduce the dose for 2 days prior to surgery and if given in the morning should hold in the morning of surgery and restart after the procedure or next morning.

15.8.4.8.1. VRIII is indicated in patients who are not well controlled but in whom surgery cannot be postponed and Patient who anticipated to have long starvation period (two or more missed meals)

15.8.4.8.2. Preparation of VRIII- 0.5 ml of soluble insulin (containing 50 U) in 49.5ml of 0.9% sodium chloride solution in a 50 ml syringe in infusion pump.

15.8.4.8.3. If the patient is already on a long-acting insulin analogue (e.g., Levemir, Lantus) these should be continued at 80% of the usual dose.

15.8.4.8.4. Fluids to run alongside the VRIII

For patients requiring VRIII, to provide glucose as a substrate to prevent ketogenesis, as well as to optimize intravascular volume status and maintain plasma electrolytes within the normal range, glucose 5% in saline 0.45% pre-mixed with either potassium chloride 0.15% (20 mmol/L) or 0.3% (40 mmol/L), depending on the presence of hypokalaemia (< 3.5 mmol/L) should be administered. (Substrate solution- 5% glucose in 0.45% saline solutions are available)

- If the solution is not available, 4% glucose in 0.18% saline (100 ml of 0.9% saline in 400 ml of 5% dextrose) and potassium chloride 0.15% (20 mmol/L) or 0.3% (40 mmol/L), depending on the presence of hypokalaemia (< 3.5 mmol/L) can be used instead, but need daily electrolyte assessment. Rate of substrate infusion must be set to deliver hourly fluid requirement of individual.

15.8.4.9 CPG is monitored hourly to adjust the rate of insulin infusion. (Follow table 15.9 to adjust the rate of infusion). If the blood glucose remains over 220 mg/dL for 3 consecutive readings and is not dropping by 55mg/dl/hour the result should be rechecked. Scale should be changed as shown in the table below:

Table 15.9 The use of variable rate intravenous insulin infusion (VRIII)

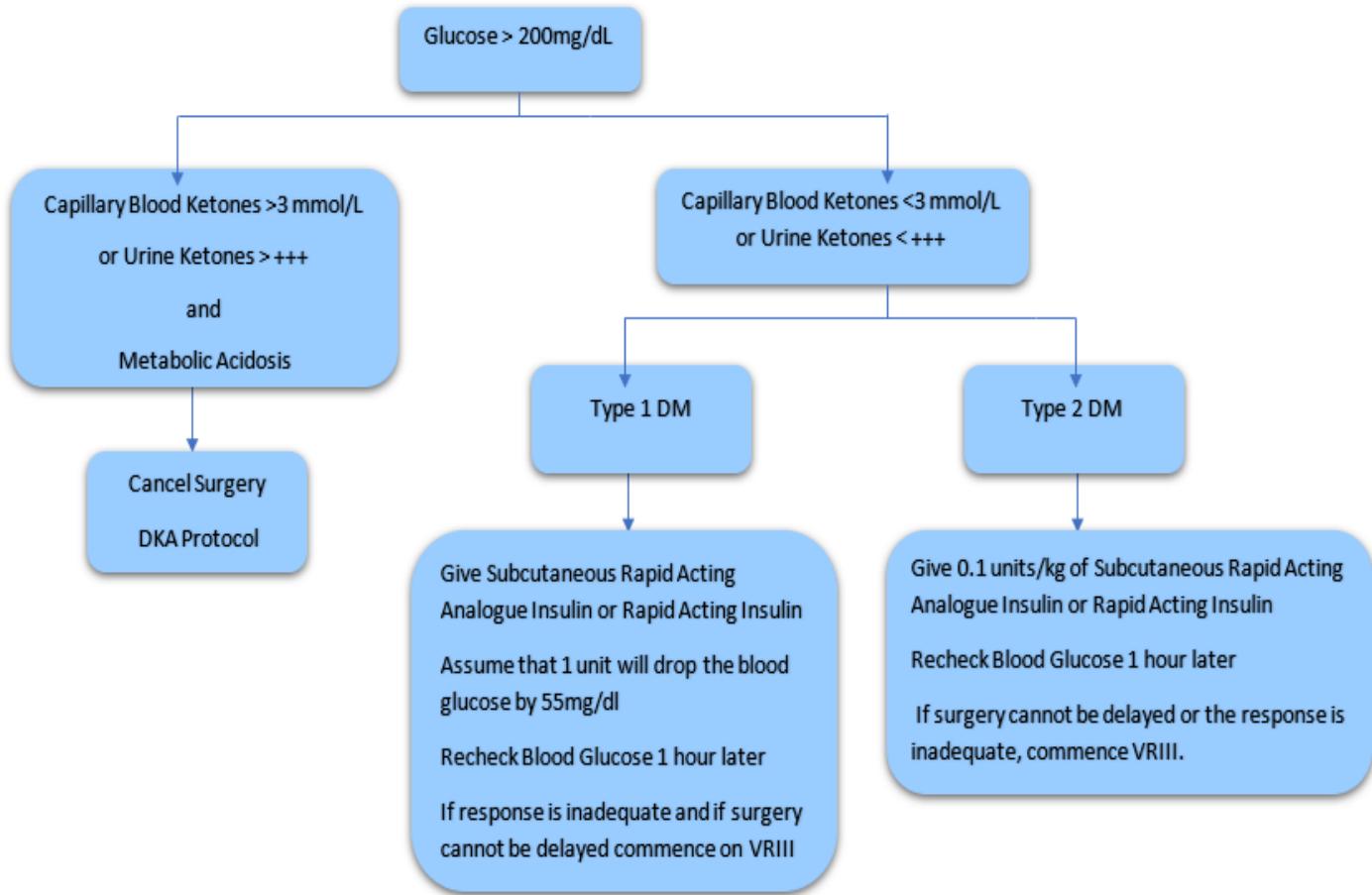
Glucose mg/dl	Insulin Rates (ml/hr)						
	Standard Rate (start on standard rate unless indicated)		Reduced Rate (for use in insulin sensitive patients; needing <24U/day)		Increased Rate (for use in insulin resistant patients; needing >100U/day)		Customized scale
	no basal insulin	basal insulin continued	no basal insulin	basal insulin continued	no basal insulin	basal insulin continued	
<70	0.5 ml/hr With 100ml IV 20% glucose	0 ml/hr With 100ml IV 20% glucose	0.2 ml/hr With 100ml IV 20% glucose	0 ml/hr With 100ml IV 20% glucose	0.5 ml/hr With 100ml IV 20% glucose	0 ml/hr With 100ml IV 20% glucose	
70-110	0.5 ml/hr and consider 50ml IV 20% glucose*	0 ml/hr and consider 50ml IV 20% glucose*	0.2 ml/hr and consider 50ml IV 20% glucose*	0 ml/hr and consider 50ml IV 20% glucose*	0.5 ml/hr and consider 50ml IV 20% glucose*	0 ml/hr and consider 50ml IV 20% glucose*	
111-140	1	1	0.5	0.5	2	2	
141-220	2	2	1	1	4	4	
221-290	4	4	2	2	6	6	
291-360	5	5	3	3	7	7	
361-430	6	6	4	4	8	8	
>431	8	8	6	6	10	10	
>431	Ensure insulin is running and not measuring an artifact						

*if the patient is pre-operative, sedated or anaesthetised, or there has been a rapid fall to a CBG between 70 and 110mg/dl: give 50ml of 20% glucose IV to prevent the CBG falling to below 4.0 mmol/L

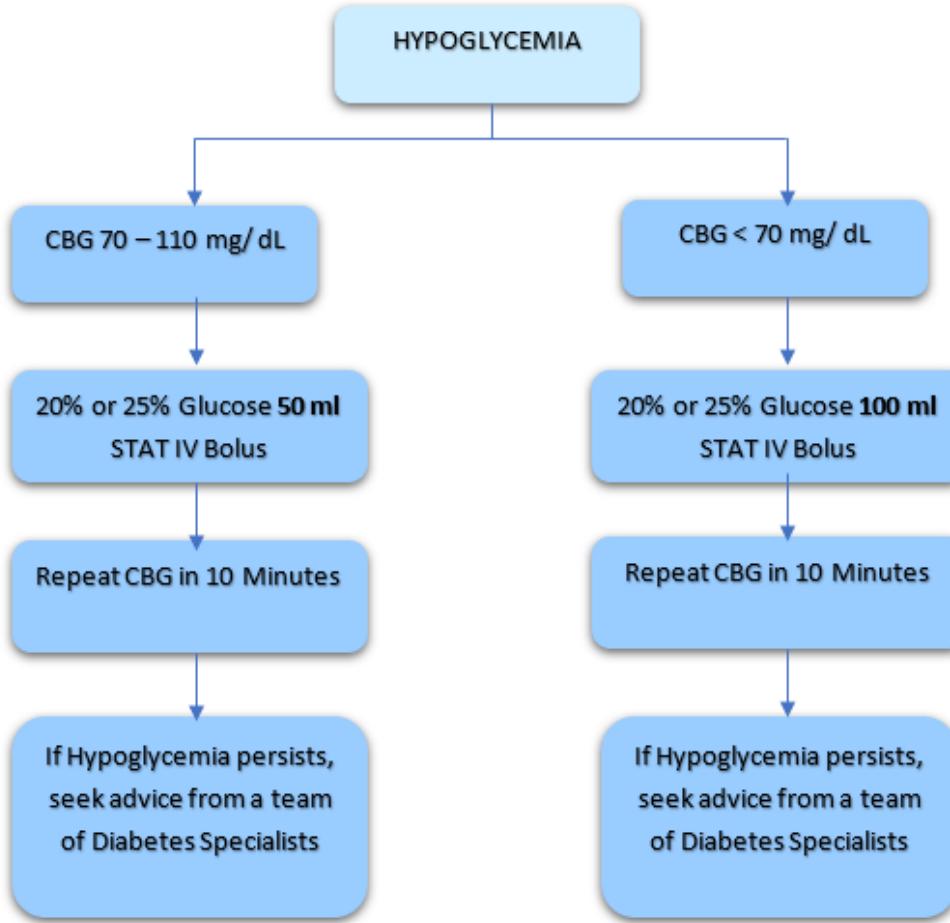
15.8.4.10 Management of peri-operative hyperglycemia should follow diagram 15.7

- **Procedures are generally cancelled when blood glucose >400 mg/dl.**

15.8.4.11 Management of peri-operative hypoglycaemia should follow diagram 15.8



15.7: Management of peri-operative hyperglycemia



15.8: Management of perioperative hypoglycaemia

This guideline is not for patients on diet alone or those who do not have the risk of hypoglycaemia

- It is not recommended to stop VRIII in type 1 diabetes. If stopped it should be restarted when the CBG is 90 mg/dl.

15.8.5 Intra-operative care and management

15.8.5.1 The aim of intra-operative care is to maintain good glycemic control. An intra-operative BG range of 110- 180 mg/dl should be aimed for. The CBG should be checked before induction of anesthesia and monitored regularly during the procedure (at least hourly, or more frequently if the results are outside the target range). In critically ill patients blood sugar target should be 140-180 mg/dl.

15.8.5.2 When blood sugar 180-220 mg/dl more frequent monitoring is needed.

15.8.5.3 When blood sugar >220, Correct intra-operative hyperglycemia using additional subcutaneous rapid acting insulin or VRIII after excluding DKA, follow diagram 15.7

15.8.5.4 Intra-operative hypoglycaemia management should follow the appropriate diagram 15.8

15.8.6 Post-operative Diabetes care

15.8.6.1 Post-operative glucose targets in an awake patient not on VRIII is 70- 220 mg/dl. If on VRIII it is 110-180 mg/dl. In critically ill patient's glucose target should be 140-180n mg/dl.

15.8.6.2 Encourage early return to normal eating which will allow the use of the usual diabetes medication of the patient.

15.8.6.3 Inspect feet and pressure areas regularly.

15.8.6.4 Consult the specialist team if the blood glucose levels are outside the acceptable range.

15.8.6.5 Ambulatory procedures- Glucose should be monitored before discharge to screen for hypoglycaemia. Patient should be instructed to resume oral agents or subcutaneous agents when they start eating.

15.8.6.6 For post-surgical patients admitted to ICU - VRIII insulin infusion is the best method to control hyperglycemia. In addition, subcutaneous basal insulin can be given along with VRIII insulin that help smooth transition to subcutaneous insulin regime.

Transitioning from VRIII insulin to subcutaneous insulin is done once patient is stable, off vasopressors, extubated and eating or being maintained on stable regime of enteral or parenteral nutrition. The transition should take place when the next meal- related subcutaneous insulin dose is due e.g. with breakfast or lunch (follow table 15.10).

Table 15.10: Transitioning from VR111 Insulin to Subcutaneous Insulin

For patients on Basal bolus regime (BBR)	The fast-acting insulin should be injected subcutaneously with the meal and the intravenous insulin and fluids discontinued 30-60 minutes later
For patient on twice daily pre-mixed Insulin	The insulin should be re-introduced before breakfast or before the evening meal. The VRIII should be maintained for 30 to 60 minutes after the subcutaneous insulin has been given.
For Insulin-naïve patients	<p>Calculation of Estimated Total Daily Dose (TDD) of insulin</p> <p>Calculate the average hourly insulin dose by totaling the last 6 hours doses on the chart and dividing by 6. This should then be multiplied by 24 to get the total daily dose (TDD) insulin.</p> <p>Give approximately 50% of the TDD in the form of long-acting insulin and divide the remaining dose to be given as rapid acting equally between pre-breakfast, pre-lunch and pre-evening meal.</p> <p>If a twice-daily pre-mixed insulin regimen is to be used, two thirds of the total daily dose should be given at breakfast, with the remaining third given with the evening meal.</p> <p>The VRIII should be maintained for 30 to 60 minutes after the subcutaneous insulin has been given.</p>
For the patient on a continuous subcutaneous insulin infusion	The subcutaneous Insulin infusion should be recommenced at their normal basal rate. The VRIII should be continued until the next meal bolus has been given.

- 15.8.6.7** For **patients transferred to inpatient floor (ward)** who can be placed back on their pre-operative regimen, if HbA1c <7.5% pre-operatively, once the patient is able to eat and drink. Dose adjustments may be required as the insulin requirement may change as a result of postoperative stress, infection or altered food intake.
- 15.8.6.8** For **patients with stress induced hyperglycemia and normal HbA1c**, who are on low insulin drip rate <2U/hr , basal insulin may not be required, and they can be transitioned to correctional scale depending on blood glucose level. On discharged they should be reviewed in 1 month with repeat FBS.
- 15.8.6.9** Provide patient education to ensure safe management of diabetes on discharge

Chapter 16

Lifestyle modification

16.1 Exercise in diabetes

16.1.1 Introduction

Exercise or planned structured physical activity, can help people with diabetes achieve number of benefits, including increased cardiorespiratory fitness, increased vigour, improved glycemic control, decreased insulin resistance, improved lipid profile, blood pressure reduction and maintenance of weight loss, therefore physical activity and exercise recommendations should be tailored to meet the specific needs of each individual.

Type of exercise and physical activity.

- Aerobic exercise involves repeated and continuous movement of large muscle groups. Activities such as walking, cycling, and swimming rely primarily on aerobic energy producing system.
Moderate intensity aerobic activities range from 3-6 METS and include brisk walking, jogging, dancing, light cycling, gardening, swimming (slow), treadmill (slow) and domestic chores.
Vigorous intensity activities (>6 METS) include running, climbing stairs or hill walking, fast cycling, swimming (fast) and most competitive sports and games.
- Interval training is a type of aerobic exercise training based on alternating between short periods of vigorous intensity exertion and periods of rest or lower intensity. e.g., running or cycling fast alternatively with short recovery period of rest or low intensity activities for 30 seconds to 3 minutes.
- Resistance (strength) training involves brief repetitive exercise with weights, weight machines, resistance bands or one's own body weight (e.g., push-ups) to increase muscle strength and or endurance.
- Balance training exercises are done to improve posture, balance, joint position sensation and coordination.
E.g., standing without support, tandem walking, heel walking, tip toe walking, ball throwing in a single leg
- Yoga is a type of exercise that incorporates elements of resistance. It reduces stress, improves balance, flexibility, and glycemic control.
- Aquatic exercise can have similar benefits as other forms of exercise and help minimize barriers from conditions such as osteoarthritis. Aquatic exercise can include walking briskly in water, swimming or many varieties of activity.

16.1.2 It is recommended that making specific exercise goals and facilitating to achieve these will benefit diabetes patients.

Setting specific exercise goals, problem solving for potential barriers to physical activity, providing information on when and where to exercise and self-monitoring advice will increase physical activity and improve HbA1c.

- 16.1.3 It is recommended to accumulate at least 150 minutes per week of moderate intensity aerobic exercise each week, spread over 3 -5 days of the week or 75 minutes of vigorous intensity aerobic exercise in a week with no more than 2 consecutive days without exercise to improve glycemic control in T2DM.
- 16.1.4 It is recommended at least 150 minutes per week of aerobic exercise and dietary changes resulting in weight loss of 5-7% to prevent or delay the onset of T2DM in at risk population including pre-diabetes.
- 16.1.5 It is recommended that interval training for diabetes patients who are physically fit to increase gains in cardio-respiratory fitness in T2DM and shown to reduce risk of hypoglycaemia during exercise in T1DM.
- 16.1.6 It is recommended that resistance exercise for patients with diabetes (specially for older people) at least 2 times per week. In addition to aerobic exercise.
Resistance training in adults with T2DM improves glycemic control, decreases insulin resistance, increases muscle strength and bone mineral density, leading to enhanced functional status.
- 16.1.7 It is recommended that the use of step count monitoring with a pedometer, accelerometer or mobile applications and this can be useful in increasing physical activity.
- 16.1.8 It is suggested that patients with T2DM should decrease the amount of time spent in daily sedentary behavior.
Prolonged sitting should be interrupted with bouts of light activity every 30 min for blood glucose benefits, at least in adults with T2DM.
Sedentary behaviour includes prolonged sitting, television viewing, working on a computer and driving.
- 16.1.9 It is suggested that patients with diabetes >40 years of age who wishes to undertake vigorous or prolonged exercise (e.g., competitive running, long distance running, HIIT), to be assessed for conditions that might place them at increased risk for an adverse event.
- 16.1.10 It is suggested that patients with peripheral neuropathy who do not have active foot ulcers could safely participate in moderate weight bearing exercise with appropriate foot protection.
Studies suggest patients with peripheral neuropathy in feet, who participate in daily weight bearing activity, are at decreased risk of foot ulceration compared to those who are less active.
- 16.1.11 It is suggested patients with diabetes autonomic neuropathy be carefully monitored during exercise.
Patients with diabetes autonomic neuropathy are at risk of haemodynamic instability due to abnormal heart rate and blood pressure in response to exercise.
- 16.1.12 It is recommended not to restrict normal physical activity in patients with any degree of diabetic retinopathy but patients with proliferative diabetic retinopathy may need to

restrict vigorous aerobic exercise and resistance training due to risk of vitreous hemorrhage. (See Diabetic Retinopathy 12.1.5.4.)

Hypoglycaemic episodes during and after exercise in patients with T1DM could be prevented effectively with following strategies

- It is suggested to monitor blood sugar at the beginning and end of exercise in patients who are initiating an exercise program or patients who are having fluctuating blood sugar levels to avoid hypoglycaemia.
- Reducing the bolus dose of the insulin that is most active at the time of exercise.
- Performing resistance exercise before aerobic exercise or interval training during aerobic exercise.
- Increasing carbohydrate consumption prior to, during and after exercise.
- What to do depending on starting blood sugar level

BOX 16.1

Starting blood sugar Level	Recommendation
• <90 mg/dl (5 mmol/L)	<ul style="list-style-type: none">• Do not exercise• Ingest 10-20g of glucose before exercise. Delay exercise until CBS >90mg/dl
• 90-144 mg/dl (5-8 mmol/L)	<ul style="list-style-type: none">• Ingest 10g of glucose before exercise• Exercise can be started
• 144-250 mg/dl (8-13.8 mmol/L)	<ul style="list-style-type: none">• Low to moderate intensity exercise can be started
• 250-300 mg/dl (Ketone negative)	<ul style="list-style-type: none">• Low to moderate intensity exercise can be allowed
• >300 mg/dl(16.8 mmol/L)	<ul style="list-style-type: none">• Do not exercise

Physical activity and pregnancy with diabetes

16.1.13 It is suggested that women with preexisting diabetes to engage in regular physical activity prior to and during pregnancy as advised by the treating specialist.

Exercise Prescription Example

- Aerobic exercise
 - Start by walking at a comfortable pace for as little as 5 to 15 minutes at one time.
 - Gradually progress over 12 weeks to up to 50 minutes per session of brisk walking (including warm up and cool down).

- Alternatively, short exercise sessions in the course of a day, e.g., 10 minutes 3 times a day after meal, can replace a single longer session of equivalent length and intensity.
- Resistance exercise
 - Choose approximately 6 to 8 exercises that target the major muscle groups in the body.
 - Gradually increase the resistance until the person could perform 3 sets of 8 to 12 repetitions for each exercise, with 1 to 2 minutes of rest between sets.
Progressive resistance training (PRT) has proven more beneficial blood sugar control effects when combined with aerobic exercises.
 - The best evidence supports strength training with weight machines and free weights. Free weights resistance exercises have additional benefits of posture and balance control.
 - If individual wish to begin resistance exercise, he/she should receive initial instruction and periodic supervision by a qualified exercise specialist to maximize benefit, while minimizing risk of injury.
- Interval exercise
 - Exercise performed in alternating between high intensity and low intensity, can be used by participants who have trouble sustaining continuous aerobic exercise, or can be used to shorten total exercise duration or increase variety.
 - Try alternating between 3 minutes of fast walking and 3 minutes of slow walking.
 - A form of interval training, HIIT can be performed through shorter intervals of higher intensity exercise (e.g., 30 seconds to 1 minute at near maximum intensity alternating with 1-3 minutes of lower intensity activity) and can be performed with walking, running or other modalities of exercise.
 - Start with just a few intervals and progress to longer durations by adding additional intervals.
- Gauging intensity of exercise with heart rate
 - Moderate intensity exercise - 50 % to 70% of your maximum heart rate.
 - Vigorous intensity exercise – 70% to 85% of your maximum heart rate.
- Other types of exercises such as yoga, Tai chi and aquatic exercise may also benefit individuals.

16.2 Dietary management

16.2.1 Provide individualized medical nutrition therapy delivered by a healthcare professional trained on dietary management of diabetes.

16.2.2 Consider the person's daily routine, culture and spiritual practices when customizing an eating pattern.

16.2.3 Focus on a specific eating pattern. Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet are two evidence-based eating patterns for dietary management of T2DM. The DASH diet emphasizes a high intake of fruits, vegetables, whole grains and low-fat dairy products, while the Mediterranean diet focuses on a high intake of

vegetables, fresh fruits, whole grains, fish and seafood, legumes, nuts and extra virgin olive oil, a moderate intake of dairy products and a restriction in intake of red and processed meats.

Since there is a paucity of evidence for a specific eating pattern in the Sri Lankan context, the plate method, which encourages a high intake of non-starchy vegetables and protein foods such as fish, white meat and pulses, while reducing the intake of rice, can be recommended when giving dietary advice to Sri Lankan adults with T2DM. Encourage to consume fruits as a snack in-between meals to minimize the glycemic load of main meals. Reduce the intake of foods with saturated and trans-fat. A guide to healthy eating for patients with diabetes is provided in **Annexure 7**.

- 16.2.4 Encourage carbohydrate intake from high-fiber foods such as whole grains, vegetables, fruits, and legumes. Foods lower in glycemic load should be advised over other sources, especially those containing sugars.
- 16.2.5 Individualize the carbohydrate content for the eating pattern, minimizing the risk of hypoglycaemia for individuals on insulin or an insulin secretagogue.
- 16.2.6 Integrate the dietary management with physical activity, behavior modification and weight management where indicated.
- 16.2.7 Offer dietary advice considering blood glucose control, weight management and cardiovascular risk reduction, when giving dietary advice to adults with T1DM.
- 16.2.8 Offer detailed education about carbohydrate counting and/or carbohydrate exchange system when providing an eating pattern for adults with T1DM. A carbohydrate counting book should be used for this purpose. Carbohydrate content of some commonly consumed food items are given in **Annexure 7**.
- 16.2.9 Educate patients about myths related to certain 'foods good for diabetes. Some common myths related to diabetes and diet are given in **Annexure 7**.

16.3 Weight management

- 16.3.1 For adults with diabetes who are overweight or obese (BMI more than or equal to 23 kgm⁻²), recommend a weight loss target of 5–10% of current body weight in 3–6 months. Even weight loss of less than 5% still is of benefit.
- 16.3.2 Offer a structured lifestyle modification program comprising healthy eating, behavior modification and physical activity, preferably delivered by a trained clinical nutritionist where feasible.
- 16.3.3 For individuals with normal weight and ones who successfully lost additional weight, advice to maintain their weight.
- 16.3.4 Discuss the potential of diabetes remission via weight loss in overweight or obese adults in whom T2DM was diagnosed less than 6 years ago.
- 16.3.5 Offer a comprehensive lifestyle modification program targeting 10–15% weight loss in 3–6 months, delivered by a trained clinical nutritionist for diabetes remission.

Chapter 17

Diabetes in different cultural backgrounds

Sri Lanka has a multi-religious, multicultural society. The diabetic population of Sri Lanka shares the same characteristics. Various cultural and religious practices pertaining to behaviour, especially diet, can affect satisfactory control of diabetes. The objective of this guidelines is to develop a tailor-made set of recommendations to ensure safety while controlling diabetes ideally without affecting cultural and religious practices of the individual.

Since clinical evidence is lacking, many of these recommendations are based on pharmacokinetics and pharmacodynamics of medications and refined by consensus of experts.

General recommendations

- Cultural/ religious background and practices should be explored actively in all patients with diabetes.
- Cultural/ religious practices regarding dietary habits (E.g., seasonal fasting) should be elucidated and noted in records for easier reference during follow-up.
- Cultural/ religious practices regarding dietary habits should be respected and medications should be tailor-made to suit the dietary habits.
- If cultural/ religious practices obstruct good glycaemic control significantly (E.g., frequent hypoglycaemia during fasting) despite adhering to these recommendations, attempts should be made to change the practices for the best interest of the individual.

17.1 Fasting in Buddhism

17.1.1 Diet

- While eating patterns of Buddhist monks vary significantly depending on their spiritual practices, many monks take only two solid meals a day, before dawn and at noon. Between noon and dawn, fluids and some food items can be consumed. The meal taken at noon is the main meal.
- This dietary pattern increases the risk of hypoglycaemia in patients with diabetes, especially if only low-calory fluid is consumed between noon and dawn.
- Similarly, there is a risk of hyperglycaemia and obesity in those who consume a large main meal and take sugary drinks between noon and dawn to prevent possible hypoglycaemia.
- They have a limited option to plan their diet as many Buddhist monks' meals are offered by devotees. (Dana) Thus, their calorie intake varies from day-to-day.

Recommendations

- A consistent diet should be consumed as much as the circumstances allow.
- The two main meals should be based on the "healthy plate", similar to lay individuals with diabetes. (Refer to annexure 7, section 16.2)
- For those do not consume solid food after noon meal, discuss the possible alternate sources of energy permitted by "vinaya" they adhere to.
- Avoid consuming high calory food such as sweetened beverages and Jaggery between noon and dawn.

17.1.2 Physical activity

Getting adequate physical exercise is a challenge for Buddhist monks as many forms of outdoor exercise such as jogging, swimming, and cycling are considered not appropriate for them.

Recommendations

It is recommended Buddhist monks engage in regular physical activity at least 30 minutes a day. Brisk walking and sweeping the compound (*Maluwa amadeema*) can be suggested.

17.1.3. Medications

17.1.3.1. Oral hypoglycaemic drugs

- Metformin is the preferred first line therapy
- Metformin has a low risk of hypoglycaemia and weight neutral, making it suitable for eating patterns of Buddhist monks
- Metformin can be prescribed once-a-day, twice a day or three times a day.
- It is not necessary to take a solid meal at night with metformin since risk of hypoglycaemia with metformin is low.
- It is beneficial to increase the dose of metformin until the highest recommended/tolerated dose is reached
- Extended-release metformin can be used once or twice a day
- Choice of the second oral agent in Buddhist monks is based on similar factors to that of lay individuals with diabetes except risk of hypoglycaemia is higher in Buddhist monks.
- DPP4 inhibitors have a low risk of hypoglycaemia and weight neutral, making good choice to use after metformin in Buddhist monks with diabetes.
- It is recommended to use DPP4 inhibitors once a day.
- DPP4 inhibitors can be used any time of the day. It is not necessary to take a solid meal if DPP4 inhibitor is taken at night.
- DPP4 inhibitor dose can be increased safely until the highest recommended/tolerated dose is reached.
- Risk of hypoglycaemia and obesity needs to be considered if a decision is taken to use sulphonylureas in Buddhist monks.
- Sulphonylureas, with a lower risk of hypoglycaemia (glimepiride, gliclazide) are recommended in preference over sulphonylureas with a higher risk of hypoglycaemia (glibenclamide)
- Sulphonylureas can be given safely with one of the two main meals.
- If a night dose of a sulphonylurea is prescribed, it should be taken with adequate amount of calory in the form of an appropriate meal.
- Increasing the dose of the sulphonylurea to maximum recommended dose needs to be done with caution.
- Thiazolidinediones can be used any time of the day. It is not necessary to take a solid meal if a thiazolidinedione is taken at night as the risk of hypoglycaemia is low.
- Thiazolidinedione dose can be increased safely until the highest recommended/tolerated dose
- SGLT2i can be used safely once a day, either combined with one of the main meals or at night as the risk of hypoglycaemia is low.

- SGLT2i dose can be increased safely until the highest recommended dose is reached.
- Adequate fluid intake should be ensured when using SGLT2 inhibitors: especially between noon and dawn.
- Acarbose is a useful drug to use in Buddhist monks, especially for those who has high PPPG.

17.1.3.2. Insulin

- Indications to start insulin in Buddhist monks are similar to that of a lay individual with diabetes; initiation of insulin therapy should not be delayed due to concerns about hypoglycaemia.
- However, self-monitoring of blood glucose is highly recommended, especially for those who take only low energy liquids between noon and dawn.
- Choice of insulin is individualized according to glycaemic status and meal pattern.
- Basal insulin can be given safely at bedtime as risk of hypoglycaemia is low.
- If there is inadequate control with basal insulin, rapid acting insulin can be added to noon meal and/or morning meal. An alternative is to use premixed insulin with morning meal.
- Adding a rapid acting insulin or pre-mixed insulin at night has to be done with extreme caution, after ensuring adequate amount of calory intake.

17.2 Management of diabetes during Ramadan

Many Muslims in Sri Lanka fast during the Ramadan period which falls in months of April and May. During Ramadan, Muslims fast daily from dawn to sunset. There is strict fasting that requires abstinence from food and drink including swallowed medicine or water. Fasting starts after Suhur (morning meal) and ends with Iftar (evening meal)

Due to the changes in lifestyle during Ramadan, there is increased risk of hyperglycaemia, hypoglycaemia and diabetic metabolic emergencies. (DKA and HHS)

Fasting in Ramadan can be used to achieve health benefits such as weight loss especially if it is done in a scientific way, with involvement of the patient and clinician.

17.2.1 General recommendations

- It is recommended that plans for Ramadan fasting be discussed fully with the patient 4-6 weeks in advance.
- It is recommended that diabetic patients who wish to fast during Ramadan be risk stratified. Patients with high risk are,
 - Recent (within 3 months) DKA or HHS
 - Severe hypoglycaemia within last 3 months
 - Recurrent hypoglycaemia
 - Hypoglycaemia unawareness
 - Previous Ramadan experience of hypoglycaemia or hyperglycaemia
 - Poor glycaemic control ($HbA1c >10\%$)
 - Pregnancy
 - Multiple co-morbidities
- It is recommended that high risk individuals with diabetes be advised not to fast.

- It is recommended that patient's wish to fast despite being in high risk be respected, provided satisfactory discussion regarding risk of fasting is carried out.
- It is recommended that fasting be broken if there are symptoms of hypoglycaemia or acute intercurrent illness.

17.2.2 Diet

Unhealthy eating patterns leading to hyperglycaemia during the non-fasting period will lead to weight gain. Consumption of particularly large meal at Iftar, sugar loaded desserts and fried food are the contributing factors.

Recommendations

- It is recommended to adhere to a healthy meal plan during Ramadan. (Refer to **Annexure 7 and Section 16.2**)
- Recommendations to prevent unhealthy eating patterns are
 - Avoiding sugary desserts
 - Consuming carbohydrates with high fibre content and low glycaemic index
 - Taking morning meal as late as possible
 - Maintaining hydration during non-fasting period by taking adequate amounts of water and non-sweetened beverages
 - Breaking fast with water to rehydrate and eat small number of calories (e.g., 1 or 2 dates) to raise blood glucose slowly

17.2.3. Physical Activity

Recommendations

- It is recommended that at least moderate physical activity be continued 30 minutes-a-day during Ramadan fasting
- It is recommended that vigorous physical activity be avoided during fasting hours as it increases risk of hypoglycaemia and dehydration

17.2.4. Self-Monitoring of Blood Glucose (SMBG)

Recommendations

- It is recommended to do SMBG several times a day, both during fasting and non-fasting time; especially when a patient falling to high-risk category and has chosen to continue Ramadan fasting
- Fasting should be broken if blood glucose <70mg/dL (3.9 mmol/L)
- Dose adjustments to oral hypoglycaemics and insulin needs to be done periodically based on SMBG results.

17.2.5 Medications

17.2.5.1. Oral hypoglycaemic drugs

Since prolonged fasting increases the risk of hypoglycaemia and taking extra-large meals on breaking the fast can lead to hyperglycaemia, therefore modifications to their oral hypoglycaemic medications and insulin are needed.

There is a large body of evidence regarding safety and efficacy of oral hypoglycaemic drugs during Ramadan. The evidence consistently shows risk of hypoglycaemia is high with sulphonylureas when compared with DPP4 inhibitors, SGLT2 inhibitors and GLP 1 receptor agonists. Out of sulphonylureas, hypoglycaemia risk was low with gliclazide and glimepiride, when compared with glibenclamide.

These observations are consistent with pharmacokinetics and pharmacodynamics of these medications.

Interestingly, there are no evidence regarding the use of metformin in Ramadan, most likely due to its well-known safety record.

Recommendations

- As metformin has a low risk of hypoglycaemia, the dose changes are not needed for those who take metformin once or twice a day.
- For patients taking metformin three times a day, noon dose has to be withheld and taken with evening meal to prevent gastric irritation.
- Doses of slow-release metformin need not be changed
- It is reasonable to change glibenclamide to gliclazide or glimepiride during the planning stage of Ramadan fasting.
- Patients taking sulphonylurea once-a-day can take the same dose with iftar (evening meal). However, the dose may be reduced if there is good glycaemic control, especially in those with high risk of hypoglycaemia.
- Patients taking sulphonylurea twice-a-day can take the same evening dose with iftar. Morning dose may be reduced if there is good glycaemic control.
- Patients on acarbose, DPP4 inhibitors, thiazolidinediones or SGLT2i need not have dose adjustments. However, if the glycaemic control is well maintained, drug doses may be reduced, especially in those with high risk of hypoglycaemia. Patients on once-a-day dosing can take it with iftar.
- Patients on SGLT2i should take extra fluids during non-fasting period.
- Consider changing SGLT2i to a different oral hypoglycaemic drug or insulin in elderly and individuals with a risk of hypotension (e.g., on multiple anti-hypertensive medications or diuretics) during the planning phase of Ramadan fasting.

17.2.5.2. Insulin

- SMBG is recommended in patients on insulin, especially in high-risk patients who wished to fast. Dose adjustments needs to be done according to glycaemic control.
- Patients on basal insulin can take the same dose Iftar (evening meal). However, the dose may be reduced if there is very good glycaemic control and/or risk of hypoglycaemia is high.
- Patients on pre-mixed insulin once-a-day can take the usual dose at iftar.
- Patients on unequal doses of pre-mixed insulin twice-a-day can take the lower dose with the morning meal and higher dose with evening meal.

- Patients on prandial rapid action insulin can have the usual evening dose at Iftar. Noon dose should be omitted, and morning dose may be reduced.

17.3 Fasting in Hinduism

The practice of fasting is a major part of Hinduism and can range from light restriction to extreme abstention. However, fasting in Hinduism is not an obligation but an individual decision. Therefore, the choice of days, duration and extent of fasting depend on individual, family, and community. Extreme fasting is not commonly seen in Sri Lanka.

Skanda Sashti festival, Nawarathri festival and fasting associated with Ayyappan swami pilgrimage are some examples where Hindus of Sri Lanka engage in fasting. In addition, there are many regional festivals where devotees choose to fast.

Fasting of Hindu devotees with diabetes can affect their glycaemic control.

17.3.1. Recommendations

- Possibility of fasting should be elucidated at every encounter with a Hindu individual with diabetes. This is especially important since fasting in Hindu devotees is highly personalized.
- If there is going to be extreme fasting or prolonged fasting it is recommended to prepare an individualized plan with consultation of specialist team well in advance.
- Every effort should be made to change medication to suit the individual's religious practice regarding diet. However, if fasting affects the individual's health significantly, attempts should be made to change the practice for the best interest of the patient.
- Frequent SMBG is recommended during fasting, especially on those taking sulphonylureas or insulin.
- If fasting is limited to two meals per day, same doses of metformin, DPP4 inhibitors and SGLT2i can be used.
- If fasting is limited to two meals per day, it is reasonable to reduce the doses of sulphonylurea.
- Adequate fluid intake needs to be ensured in patients taking SGLT2i during fasting.
- If fasting is restricted to one meal per day an individualized plan has to be prepared considering patient's characteristics and current glycaemic control.

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Annexures

Annexure 1

Page 1 of 3

**Portland Continuous Intravenous Insulin Protocol Floor TARGET BLOOD GLUCOSE 100 to 150mg/dl
Version 2008.1: Floor PHASE 3**

1. Start "Portland Protocol" on all Diabetic Floor patients if indicated as noted below:
 - Preoperative Patients -- Start Portland Protocol for any BG >180 mg/dl, including "non-diabetic" patients
 - Postoperative Patients – Continue Portland Protocol upon transfer from ICU or restart if BG > 150 mg/dl
 - Medical Patients – Start protocol if NPO or on clear liquids and BG > 150 mg/dl
 - Initial BG check on admission / transfer
 - Then recheck fingerstick BG AC, 2 hours PC & HS X 24 hours to determine if above inclusion criteria are met
 - Send blood for Hgb A1c if not already done on admission to hospital or in the ICU.
2. Mix 1 unit Regular Human Insulin per 1 ml 0.9% Normal Saline, and start IV infusion via pump as follows:

Blood Glucose	IV Regular Insulin Syringe Bolus	Initial Regular Insulin Rate: Units/Hour	
		NIDDM or non-DM	IDDM
110 to 124 mg/dl	0	None	None
125 to 150 mg/dl	2 -- For DM patients only *	1 Unit / Hour	2 Units / Hour
151 to 180 mg/dl	4 Units	2 Units / Hour	3.5 Units / Hour
181 to 240 mg/dl	6 Units	3.5 Units / Hour	5 Units / Hour
241 to 300 mg/dl	8 Units	5 Units / Hour	6.5 Units / Hour
301 to 360 mg/dl	12 Units	6.5 Units / Hour	8 Units / Hour
Greater than 360 mg/dl	16 Units	8 Units / Hour	10 Units / Hour
3. **General Orders** for ALL patients on "Portland Protocol":
 - All intermittent (noncontinuous) IV medications should be mixed in normal saline.
 - i. Do NOT administer intermittent (noncontinuous) IV medications mixed in dextrose-containing solutions
 - Do NOT use any dextrose-containing IV solutions for maintenance IV or daily IV fluids except when TPN is required.
 - If daily steroids are required: administer as a continuous infusion over a 24-hour period.
 - i. Do NOT administer Bolus IV steroids or oral steroids while on IV insulin protocol.
4. **Protocol Duration:**
 - Surgical Patients – Continue until 9 AM of 3rd Postoperative day. Then see transition to SQ insulin / oral agent orders.
 - Medical Patients -- Continue Protocol until taking soft ADA diet or more. Then see transition to SQ insulin / oral agent orders.
 - Non-DM, euglycemic patients may stop protocol when target range maintained with <0.5 units / hour; then check BG every 2 hours X 6; then AC, 2 hours PC, and HS X 24 hours; if all BG < 150 may cease monitoring; if any BG > 150 resume Protocol.
 - Non-Diabetic Surgical Patients If continuing need for insulin exists after POD #3, and admission HgbA1c is greater than 6, ask physician to consult endocrinologist for DM workup and further follow-up orders.
5. **Transfer from ICU:** Transition to Floor (ward) version of Portland Protocol on transfer out of ICU in:
 - All hyperglycemic patients: within 3 days of operation or ICU admission, or those eating less than 50% of a regular diet.
 - Non-Diabetic Patients If continuing need for insulin exists on transfer after POD #3, and admission HgbA1c is greater than 6, ask physician to consult endocrinologist for DM workup and further follow-up orders.
6. **Protocol Cessation** permissible in:
 - Diabetic Surgical patients if more than 3 days since last operation or ICU admission AND eating more than 50% of a regular diet – Then see transition to SQ insulin / oral agent orders.
 - Non-Diabetic Surgical patients if more than 3 days since last operation or ICU admission AND eating more than 50% of a regular diet – May stop protocol without transition to SQ / Oral meds. Check BG AC 2 hours PC and HS X 48 hours
 - Diabetic Medical Patients -- Transition Off Insulin Infusion when patient has been in target range for more than 4 hours, and is eating 50% or more of a soft or regular ADA meal. See transition to SQ insulin / oral agent orders
 - Non-Diabetic Euglycemic Patients may stop protocol early If meet criteria outlined in #4 "Duration"
 - Non-Diabetic patients who remain hyperglycemic beyond the 3rd postoperative day -- Endocrinology consultation should be requested by physician (see #5 above)
7. Test Blood Glucose (BG) by finger stick, or venous line drop samples. **Frequency of BG testing** is as follows:
 - Check BG every 30 minutes when:
 - i. BG greater than 180mg/dl
 - ii. BG is less than 80mg/dl
 - iii. after drip is stopped or decreased more than 50%
 - iv. after Bolus IV Insulin dose is given.
 - Check BG every Hour when BG is 80 – 180 mg/dl
 - Check BG every 2 Hours when BG is 100 - 150, with less than 15mg/dl BG variation over 4 hours and Insulin Rate remains unchanged for 4 hours – "Stable Infusion Rate". Note – If any change in BG more than 15mg/dl, or any change in Insulin Rate more than 0.5 units: Return to checking BG every Hour.
 - During initiation of, rate change of, or cessation of any nutritional support or renal correction therapy:
 - i. Renal correction therapy = Renal Dialysis, CVVH, CVVHD, Peritoneal dialysis, etc.
 - ii. Nutritional support (enteral or parenteral) includes Tube Feedings, TPN, PPN
8. **See Page 2 For Intravenous Insulin Titration Guidelines**

ICU: May titrate Insulin Infusion between 0-30 units /hour using the following as **GUIDELINES** to rapidly (within 3 hrs) achieve and maintain BG in target range (80-120). Round insulin Infusion to the nearest tenth of a unit (0.1) when necessary.

Blood Glucose (BG)	Note: If ANY BG less than 40mg/dl or greater than 450mg/dl, obtain confirmatory laboratory BG Action:
Less Than 60	Stop Insulin: <ul style="list-style-type: none"> If not alert or if NPO: give 15 ml of D50W IV; If < 40 give 25 ml of D50W IV If alert and taking PO give 8 ounces of juice PO OR 6 glucose tablets PO Recheck BG every 30 minutes until greater than 80mg/dl If next BG is < 60mg/dl: Double amount of previous treatment; If next BG is 50 – 65 mg/dl repeat treatment When BG greater than 100mg/dl: Restart Insulin rate at 50% of previous rate & recheck BG in 30 minutes
60 to 79	Stop Insulin: <ul style="list-style-type: none"> If Previous BG greater than 110mg/dl OR if symptomatic from hypoglycemia: <ul style="list-style-type: none"> If NPO: give 15 ml of D50W IV; <OR> IF taking PO: give 4-6 ounces of juice OR 3 glucose tablets PO. Recheck BG every 30 minutes until greater than 90mg/dl If next BG remains 60 - 79 mg/dl : Repeat previous treatment When BG greater than 90mg/dl: Restart Insulin rate at 50% of previous rate & recheck BG in 30 minutes
80 to 99	<ul style="list-style-type: none"> If greater than last test: Decrease rate by 0.3 units / Hour If lower than last BG by more than 30 mg/dl: Stop drip & recheck BG in 30 minutes (see bold * order) If lower than last BG by 15 – 30 mg/dl: Decrease rate by HALF (50%) & recheck BG in 30 minutes If lower than last BG by 7 – 14 mg/dl: Decrease rate by 0.5 Units / Hour If equal to last BG or lower than last BG by less than 7 mg/dl: Decrease rate by 0.3 Units / Hour <p>*If infusion turned off, recheck BG in 30 min, when BG greater than 100mg/dl restart at 50% of previous rate & recheck BG in 30 minutes</p> <ul style="list-style-type: none"> Recheck BG every 30 minutes until greater than 90mg/dl
100 to 150 Target Range EXCELLENT! May titrate drip in ICU to maintain this range. See Suggestions:	<ul style="list-style-type: none"> If higher than last BG by more than 10mg/dl: Increase rate by 0.5 Units / Hour If lower than last BG by more than 40 mg/dl: Stop drip & recheck BG in 30 minutes (see bold ** order) If lower than last BG by 21–40 mg/dl: Decrease rate by HALF (50%) & recheck BG in 30 minutes If lower than last BG by 10-20mg/dl: Decrease rate by 0.5 Units / Hour <p>** If infusion turned off, recheck BG 30 min, if /when BG greater than 130 mg/dl restart at 50% of previous rate</p> <ul style="list-style-type: none"> If within 10mg/dl of last BG same rate ... unless the following applies: <ul style="list-style-type: none"> FOR ANY BG in this range (even if within 10 mg/dl of last test) the following ALWAYS applies: <ul style="list-style-type: none"> BG has consistently decreased each of last 4 measurements: Decrease rate by an additional 0.3 Units / Hour BG has consistently increased each of last 4 measurements: Increase rate by an additional 0.2 Units / Hour
151 to 175	<ul style="list-style-type: none"> If higher than last BG by more than 50mg/dl: Increase rate by 2 Units/Hour If higher than last BG by 20 - 50mg/dl: Increase rate by 1 Unit / Hour If higher than last BG by 0 - 20mg/dl: Increase rate by 0.5 Units / Hour If lower than last BG by 1 - 20 mg/dl: Same rate If lower than last BG by 21 - 40mg/dl: Decrease rate by 1 Unit / Hour If lower than last BG by 41 – 60 mg/dl: Decrease rate by HALF (50%) and recheck BG in 30 minutes If lower than last BG by more than 60 mg/dl: Stop drip & recheck BG in 30 minutes (see bold ** order below) <p>** If infusion turned off, recheck BG 30 min, if / when BG greater than 150mg/dl restart at 50% of previous rate</p>
176 to 200	<ul style="list-style-type: none"> If higher than last BG by more than 30mg/dl: Increase rate by 2 Units/Hour & bolus with 3 units IV If higher than last BG by 0 - 30mg/dl: Increase rate by 1 Unit / Hour & bolus with 2 units IV If lower than last BG by 1 – 20: Increase rate by 1 Unit / Hour & bolus with 2 units IV If lower than last BG by 21 to 50mg/dl: Same rate If lower than last BG by 51 – 80mg/dl: Decrease rate by HALF (50%) and recheck BG in 30 minutes If lower than last BG by more than 80mg/dl: Stop drip & recheck BG in 30 minutes (see bold ** order below) Recheck BG in 30 minutes. Repeat BG every 30 minutes until less than 175mg/dl <p>** If infusion turned off, recheck BG 30 min, if / when BG greater than 150mg/dl restart at 50% of previous rate</p>
201 to 225	<ul style="list-style-type: none"> If lower than last BG by more than 80mg/dl: Decrease rate by HALF (50%) If lower than last BG by 30 –80mg/dl: Continue same rate If lower than last BG by 0 – 30: Increase Insulin rate by 1 Unit / Hour & bolus with 2 units IV If higher than last BG by 1- 20mg/dl: Increase Insulin rate by 2 Units / Hour & bolus with 4 units IV If higher than last BG by more than 20mg/dl: Increase Insulin rate by 3 Units/Hour & bolus 6 units IV Recheck BG in 30 minutes. Repeat BG every 30 minutes until less than 175mg/dl
226 to 275	<ul style="list-style-type: none"> If lower than last BG by more than 100 mg/dl: Decrease rate by HALF (50%) If lower than last BG by 50 – 100 mg/dl: Continue same rate If lower than last BG by less than 50mg/dl OR higher than last BG: <ul style="list-style-type: none"> BOLUS with 6 units Regular Insulin IV AND Increase Insulin rate by 2 Units / Hour If BG remains 226 - 275 mg/dl and has not decreased after 3 consecutive increases in Insulin: <ul style="list-style-type: none"> Give DOUBLE previous IV BOLUS dose up to a maximum of 24 units AND DOUBLE Insulin drip rate -- up to a maximum of 20 units / hour If on 20 units/hour and no response <u>after 4 maximum boluses</u> – CALL MD for further orders Recheck BG in 30 minutes. Repeat BG every 30 minutes until less than 175mg/dl
Greater than 275	<ul style="list-style-type: none"> If lower than last BG by more than 150 mg/dl: Decrease rate by HALF (50%) If lower than last BG by 101-150mg/dl: Same rate If lower than last BG by 0- 100mg/dl OR if higher than last BG: <ul style="list-style-type: none"> BOLUS with 10 Units Regular Insulin IV AND DOUBLE Insulin rate up to a maximum of 30 units / hour If BG remains greater than 275 mg/dl and has not decreased after 3 consecutive increases in Insulin: <ul style="list-style-type: none"> Give DOUBLE previous IV BOLUS dose up to a maximum of 40 units AND DOUBLE Insulin drip rate -- up to a maximum of 30 units / hour If on 30 units/hour and no response <u>after 4 maximum boluses</u> – CALL MD for further orders Recheck BG in 30 minutes. Repeat BG every 30 minutes until less than 175mg/dl
IF BG GREATER THAN 300 for 4 CONSECUTIVE READINGS: CALL MD FOR ADDITIONAL IV BOLUS ORDERS	

Annexure 2

General Guidelines:

- **Standard drip:** 100 Units/100 ml 0.9% NaCl via an infusion device.
- Surgical patients who have received an oral diabetes medication within 24hrs should start when BG>120 mg/dL. All other patients can start when BG≥70
- Insulin infusions should be discontinued when a patient is eating AND has received 1st dose of subcutaneous insulin.

Goal BG = _____ (Usually 80-180 mg/dL)

Intravenous Fluids:

- Most patients will need 5-10GM of glucose per hour
 - D₅W or D₅W1/2NS at 100-200 ml/hr or equivalent (TPN, enteral feeds, etc)

Initiating the Infusion:

- **Algorithm 1:** Start here for most patients.
- **Algorithm 2:** For patients not controlled with Algorithm 1, or start here if s/p CABG, s/p solid organ transplant or islet cell transplant, receiving glucocorticoids, or patient with diabetes receiving >80 units/day of insulin as an outpatient.
- **Algorithm 3:** For patients not controlled on Algorithm 2. NO PATIENTS START HERE without authorization from the endocrine service
- **Algorithm 4:** For patients not controlled on Algorithm 3. NO PATIENTS START HERE.
- Patients not controlled with the above algorithms need an endocrine consult.

Algorithm 1		Algorithm 2		Algorithm 3		Algorithm 4	
BG	Units/hr	BG	Units/hr	BG	Units/hr	BG	Units/hr
<60 = Hypoglycemia (See below for treatment)							
<70	Off	<70	Off	<70	Off	<70	Off
70-109	0.2	70-109	0.5	70-109	1	70-109	1.5
110-119	0.5	110-119	1	110-119	2	110-119	3
120-149	1	120-149	1.5	120-149	3	120-149	5
150-179	1.5	150-179	2	150-179	4	150-179	7
180-209	2	180-209	3	180-209	5	180-209	9
210-239	2	210-239	4	210-239	6	210-239	12
240-269	3	240-269	5	240-269	8	240-269	16
270-299	3	270-299	6	270-299	10	270-299	20
300-329	4	300-329	7	300-329	12	300-329	24
330-359	4	330-359	8	330-359	14	>330	28
>360	6	>360	12	>360	16		

Moving from Algorithm to Algorithm:

- **Moving Up:** An algorithm failure is defined as blood glucose outside the goal range (see above goal), and the blood glucose does not change by at least 60mg/dL within 1 hour.
- **Moving Down:** When blood glucose is <70 mg/dL X 2

Patient Monitoring:

- Check capillary BG every hour until it is within goal range for 4 hours, then decrease to every 2 hours for 4hrs, and if remains stable may decrease to every 4 hours.
- Hourly monitoring may be indicated for critically ill patients even if they have stable blood glucose

Treatment of Hypoglycemia (BG<60 mg/dL)

- Discontinue insulin drip AND
- Give D₅₀W IV
 - Patient awake: 25 ml (1/2 amp)
 - Patient not awake: 50ml (1 amp))
- Recheck BG every 20 minutes and repeat 25ml of D₅₀W IV if <60mg/dL. Restart drip once blood glucose is >70 mg/dL X2 checks. Restart drip with lower algorithm (see moving down)

Notify the physician:

- For any blood glucose change greater than 100 mg/dL in one hour.
- For blood glucose >360 mg/dL

For hypoglycemia which has not resolved within 20 min of administering 50ml of D₅₀W IV and discontinuing the insulin drip.

Annexure 3



YALE INSULIN INFUSION PROTOCOL



The following insulin infusion protocol is intended for use in hyperglycemic adult patients in an ICU setting, but is not specifically tailored for those individuals with diabetic emergencies, such as diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar states (HHS). When these diagnoses are being considered, or if $BG \geq 500 \text{ mg/dL}$, an MD should be consulted for specific orders. Also, please notify an MD if the response to the insulin infusion is unusual or unexpected, or if any situation arises that is not adequately addressed by these guidelines.

Initiating an Insulin Infusion

- 1.) INSULIN INFUSION: Mix 1 U Regular Human Insulin per 1 cc 0.9% NaCl. Administer via infusion pump (in increments of 0.5 U/hr).
- 2.) PRIMING: Flush 50 cc of infusion through all IV tubing before infusion begins (to saturate the insulin binding sites in the tubing).
- 3.) TARGET BLOOD GLUCOSE (BG) LEVELS: **100-139 mg/dL**
- 4.) BOLUS & INITIAL INSULIN INFUSION RATE: Divide initial BG level by 100, then round to nearest 0.5 U for bolus AND initial infusion rate.
Examples: 1.) Initial BG = 325 mg/dL: $325 \div 100 = 3.25$, round \uparrow to 3.5: IV bolus 3.5 U + start infusion @ 3.5 U/hr.
 2.) Initial BG = 174 mg/dL: $174 \div 100 = 1.74$, round \downarrow to 1.5: IV bolus 1.5 U + start infusion @ 1.5 U/hr.

Blood Glucose (BG) Monitoring

- 1.) Check BG hourly until stable (3 consecutive values within target range). In hypotensive patients, capillary blood glucose (i.e., fingersticks) may be inaccurate and obtaining the blood sample from an indwelling vascular catheter is acceptable.
- 2.) Then check BG q 2 hours; once stable x 12-24 hours. BG checks can then be spaced to q 4 hours IF:
 a.) no significant change in clinical condition AND b.) no significant change in nutritional intake.
- 3.) If any of the following occur, consider the temporary resumption of hourly BG monitoring, until BG is again stable (2-3 consecutive BG values within target range):
 - a.) any change in insulin infusion rate (i.e., BG out of target range)
 - b.) significant changes in clinical condition
 - c.) initiation or cessation of pressor or steroid therapy
 - d.) initiation or cessation of renal replacement therapy (hemodialysis, CVVH, etc.)
 - e.) initiation, cessation, or rate change of nutritional support (TPN, PPN, tube feedings, etc.)

Changing the Insulin Infusion Rate

If $BG < 50 \text{ mg/dL}$:

- D/C INSULIN INFUSION Give 1 amp (25 g) D50 IV; recheck BG q 15 minutes.
 \Rightarrow When $BG \geq 100 \text{ mg/dL}$, wait 1 hour, then restart insulin infusion at 50% of original rate.

If $BG 50-74 \text{ mg/dL}$:

- D/C INSULIN INFUSION If symptomatic (or unable to assess), give 1 amp (25 g) D50 IV; recheck BG q 15 minutes.
 If asymptomatic, give 1/2 Amp (12.5 g) D50 IV or 8 ounces juice; recheck BG q 15-30 minutes.
 \Rightarrow When $BG \geq 100 \text{ mg/dL}$, wait 1 hour, then restart infusion at 75% of original rate.

If $BG \geq 75 \text{ mg/dL}$:

STEP 1: Determine the CURRENT BG LEVEL - identifies a COLUMN in the table:

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG $\geq 200 \text{ mg/dL}$
----------------	------------------	------------------	-----------------------------

STEP 2: Determine the RATE OF CHANGE from the prior BG level - identifies a CELL in the table - Then move right for **INSTRUCTIONS**:

[Note: If the last BG was measured 2-4 hrs before the current BG, calculate the hourly rate of change. Example: If the BG at 2PM was 150 mg/dL, and the BG at 4PM is now 120 mg/dL, the total change over 2 hours is -30 mg/dL; however, the hourly change is $-30 \text{ mg/dL} \div 2 \text{ hours} = -15 \text{ mg/dL/hr}$.]

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG $\geq 200 \text{ mg/dL}$	INSTRUCTIONS*
		BG \uparrow by $> 50 \text{ mg/dL/hr}$	BG \uparrow	\uparrow INFUSION by "2Δ"
	BG \uparrow by $> 25 \text{ mg/dL/hr}$	BG \uparrow by $1-50 \text{ mg/dL/hr}$ OR BG UNCHANGED	BG UNCHANGED OR BG \downarrow by $1-25 \text{ mg/dL/hr}$	\uparrow INFUSION by "Δ"
BG \uparrow	BG \uparrow by $1-25 \text{ mg/dL/hr}$, BG UNCHANGED, OR BG \downarrow by $1-25 \text{ mg/dL/hr}$	BG \downarrow by $1-50 \text{ mg/dL/hr}$	BG \downarrow by $26-75 \text{ mg/dL/hr}$	NO INFUSION CHANGE
BG UNCHANGED OR BG \downarrow by $1-25 \text{ mg/dL/hr}$	BG \downarrow by $26-50 \text{ mg/dL/hr}$	BG \downarrow by $51-75 \text{ mg/dL/hr}$	BG \downarrow by $76-100 \text{ mg/dL/hr}$	\downarrow INFUSION by "Δ"
BG \downarrow by $> 25 \text{ mg/dL/hr}$ <i>see below†</i>	BG \downarrow by $> 50 \text{ mg/dL/hr}$	BG \downarrow by $> 75 \text{ mg/dL/hr}$	BG \downarrow by $> 100 \text{ mg/dL/hr}$	HOLD x 30 min, then \downarrow INFUSION by "2Δ"

*D/C INSULIN INFUSION:

†VBG q 30 min; when $BG \geq 100 \text{ mg/dL}$, restart infusion @75% of most recent rate.

*CHANGES IN INFUSION RATE ("Δ") are determined by the current rate:

Current Rate (U/hr)	Δ = Rate Change (U/hr)	$2\Delta = 2X$ Rate Change (U/hr)
< 3.0	0.5	1
3.0 - 6.0	1	2
6.5 - 9.5	1.5	3
10 - 14.5	2	4
15 - 19.5	3	6
20 - 24.5	4	8
≥ 25	≥ 5	10 (consult MD)

Annexure 04

Insulin therapy for parenteral /continuous enteral feeding in the ICU

Patients receiving peripheral or central parenteral nutrition, regular insulin may be added to the solution, particularly if 20 units of correctional insulin have been required in the past 24 h, or a separate insulin infusion should be adjusted. A starting dose of 1 unit of regular insulin for every 10 g dextrose has been recommended.

Patients receiving continuous tube feedings, the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g carbohydrate per day or as a percentage of the total daily dose of insulin when the patient is being fed (usually 50–70% of the total daily dose of insulin). For patients receiving enteral bolus feedings, approximately 1 unit of regular insulin or rapid-acting insulin per 10–15g carbohydrate should be given subcutaneously before each feeding.

Annexure 5

DDD protocol for conversion from continuous intravenous insulin and glucose infusions to subcutaneous insulin and oral diet

An estimate of the combined basal and nutritional subcutaneous insulin requirements can be extrapolated from the average amount of intravenous insulin infused during the hours preceding the conversion if:

- 1) the intravenous glucose infusion is kept constant and equivalent to the amount of carbohydrate in the oral diet and
- 2) the BG level is stable in the target range between 100 and 139 mg/dL (most of the BG measurements on target for at least 24 h)

Protocol	Example
Step 1. Calculate the average insulin intravenous infusion rate in the last 12 h to obtain the mean hourly rate and multiply by 24 to get the total daily insulin requirement.	$\rightarrow 1.5 \text{ units/h} \times 24 = 36 \text{ units/24 h}$
Step 2. Halve this 24-h insulin dose to obtain the long-acting insulin analog dose and total daily rapid-acting insulin analog dose.	$\rightarrow 36 \text{ units}/2 = 18 \text{ units}$
Step 3. Give the long-acting insulin analog subcutaneous monodose 2 h before the first meal and the discontinuation of intravenous insulin and intravenous glucose infusions.	\rightarrow give glargine 18 units s.c. 2 h before the first meal and stop intravenous insulin and glucose infusions at meal
Step 4. Split the total daily rapid-acting subcutaneous insulin analog dose into 20% at breakfast, 40% at lunch, and 40% at dinner, according to a similar distribution of carbohydrates in the typical Mediterranean diet.	\rightarrow give lispro 4 units s.c. before breakfast, give lispro 7 units s.c. before lunch, give lispro 7 units s.c. before dinner

Annexure 6

Insulin administration techniques

Insulin technique is a vital component of diabetes care. It mainly includes delivering of insulin into the body (Insulin administration), insulin storage and transport.

Several **routes of administration** have been evaluated for the administration of insulin, including subcutaneous, oral, dermal, intravenous and nasal. Subcutaneous insulin therapy has been a mainstay of pharmacological diabetes management.

Insulin is effective only if administered appropriately. Several factors need to be considered before administering insulin subcutaneously such as device selection, injection sites, injection preparation, and appropriate disposal of insulin injectors and related accessories.

Device Selection

Selecting the correct device, appropriate to the person's needs, is very important in insulin administration. Various devices are available in administering insulin such as vial-and-syringe, insulin pen, jet injectors, insulin inhalers and insulin pumps. Vial-and-syringe and insulin pens are widely used in Sri Lanka as primary injecting devices. Prior to injecting insulin, You should check the compatibility of insulin with the delivery device and all related accessories.

Selection of Injection sites

- Insulin can be injected into the subcutaneous tissue of the upper arm (posterior mid third of the arm, antero-lateral side of the thigh, buttocks (upper outer quadrant), and abdomen (extending down from a line drawn 1 inch above the umbilicus to a line connecting the anterior superior iliac spines) as depicted in **Figure 1 and 2**.

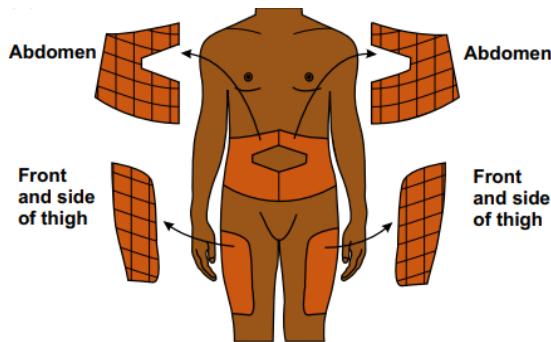


Figure 1 Figure showing the areas recommended for insulin injections as viewed from the front. They may be divided up into smaller areas, so that each area is injected not more than once a day.

Adapted from Bahendeka, S., Kaushik, R., Swai, A. B., Otieno, F., Bajaj, S., Kalra, S., ... & Karigire, C. (2019). EADSG guidelines: insulin storage and optimisation of injection technique in diabetes management. *Diabetes Therapy*, 10(2), 341-366.

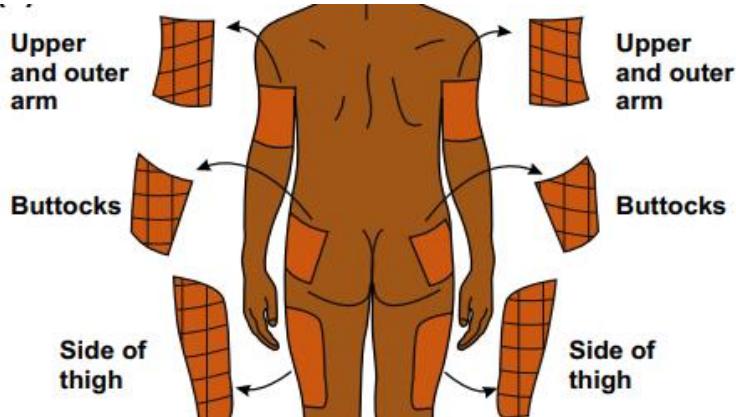


Figure 2 shows the areas recommended for insulin injections as viewed from the back

Adapted from Bahendeka, S., Kaushik, R., Swai, A. B., Otieno, F., Bajaj, S., Kalra, S., ... & Karigire, C. (2019). EADSG guidelines: insulin storage and optimisation of injection technique in diabetes management. *Diabetes Therapy*, 10(2), 341-366.

Rotation of the injection sites

- Rotation of the injection site systematically is essential to avoid lipohypertrophy, scarring of the skin which impairs the absorption of insulin into the systemic circulation (**Figure 3**).
- Each injection should be spaced fingerbreadth (2.5 cm) apart in order to minimize tissue trauma.

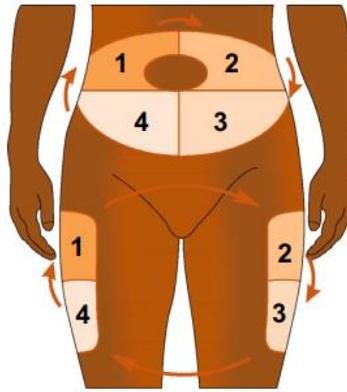


Figure 3 Figure showing a method that can be adopted to rotate insulin injections. The recommendation is to rotate the injections within one site consistently. Here the figure shows the method of rotation on the abdomen in the upper part and the thighs in the lower part

Adapted from Bahendeka, S., Kaushik, R., Swai, A. B., Otieno, F., Bajaj, S., Kalra, S., ... & Karigire, C. (2019). EADSG guidelines: insulin storage and optimisation of injection technique in diabetes management. *Diabetes Therapy*, 10(2), 341-366.

Care of Injection Site

- Proper care of injection sites should be taken to prevent complications.
- Inspect and palpate the injection sites before injecting insulin.

- Identify and avoid injecting into sites with lipohypertrophy, oedema, inflammation or signs of infection.
- Change sites of injection every day.
- Do not reuse the needle if possible; otherwise limit as much as possible. Pain during the injection would suggest blunting of the needle which indicates need for immediate replacement.
- Clean the injection site with clean water (swabbing with spirit-swabs is not recommended as it leaves the skin dry) It is essential to educate the patient to maintain the cleanliness of the skin.

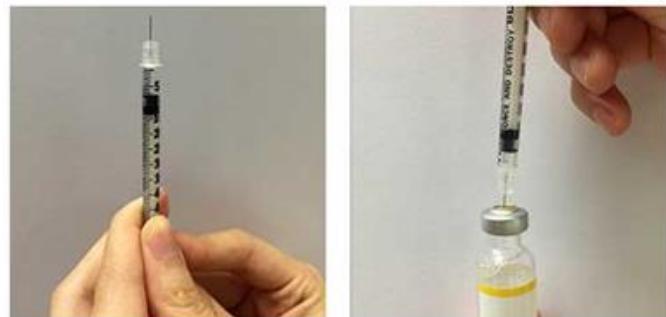
Preparation of the Injection

- Wash hands properly
 - Before insulin administration, check for expiry date, possible damage, clumping, frosting or precipitation.
 - Bring the insulin vial to room temperature by keeping it outside the refrigerator for 30 minutes
 - Ensure the correct insulin, in correct dose, and at the correct timing by rechecking the instructions
 - If using a vial, for cloudy insulin (pre-mixed & intermediate acting) gently roll the vial between the palms of the hands and /or moving the insulin up and down 20 times.
 - If using a pen, for cloudy insulin (pre-mixed & intermediate acting) invert the pen 20 times to mix the insulin well.
 - When using a syringe and vial, clean the top of the vial with an alcohol swab. Then, draw air into the syringe and push it in the vial. Next draw the insulin dose required while holding the bottle upside down.
 - Check the syringe for air bubbles prior to injection.
- If insulin preparations have to be mixed, short/acting regular insulin should be drawn first, followed by intermediate-acting insulin, so that no protamine contaminates the regular insulin vial. How to mix short-acting/regular insulin and intermediate-acting insulin is shown in **Figure 4 below**

Step 1: Draw the required amount of air (equal to dosage of intermediate-acting insulin) into the insulin syringe .Inject air into the intermediate-acting insulin vial. Do not draw out any insulin and remove the syringe and needle



Step 2: Using the same syringe and needle, draw the required amount of air (equal to the dosage for short-acting/regular insulin) into the insulin syringe. Inject air into the short-acting/regular insulin vial.



Step 3: With the insulin syringe and needle attached, turn the short-acting/regular insulin bottle upside down, with the needle bevel within the insulin, withdraw the required amount of short-acting/regular insulin into the syringe. Then do the same with the intermediate-acting insulin.



Figure 4

Mix short-acting/regular insulin and intermediate-acting insulin

Adapted from <https://www.healthxchange.sg/diabetes/essential-guide-diabetes/insulin-syringe-preparation-how-mix-short-intermediate-acting-insulin>

Administering injection

- Gently pinch a fold of skin between the thumb and forefinger.
- Do not raise a tight painful or blanched skin fold.
- Inject insulin slowly at 90° to surface of skin fold and ensure that plunger (syringe) or thumb button (pen) has been fully depressed.
(Skin fold should be raised only if longer needles are being used or if the injection is being administered to a very slim person ($BMI < 20 \text{ kg/m}^2$) or toddlers. The skin should not be squeezed so tightly that could cause pain or blanching. Injecting at 45° angle is another option in these cases).
- Count slowly to 0-30 before withdrawing needle, to obtain full dose and prevent leakage of insulin.
- Release the skin fold only after the drug has been injected and the needle withdrawn.
- Do not massage the injection site.
- Needles attached to pens should be disposed safely and immediately after use to prevent entry of air (or other contaminants) into the cartridge and/or leakage of insulin, which can affect subsequent dose accuracy
- Document dose, site and time correctly

Appropriate disposal of sharps

Inappropriate disposal may lead to needle stick injuries and spread of blood- borne infections. Therefore, appropriate disposal of injecting material is crucial.

Figure 5 shows the steps that should be taken when insulin is injected.

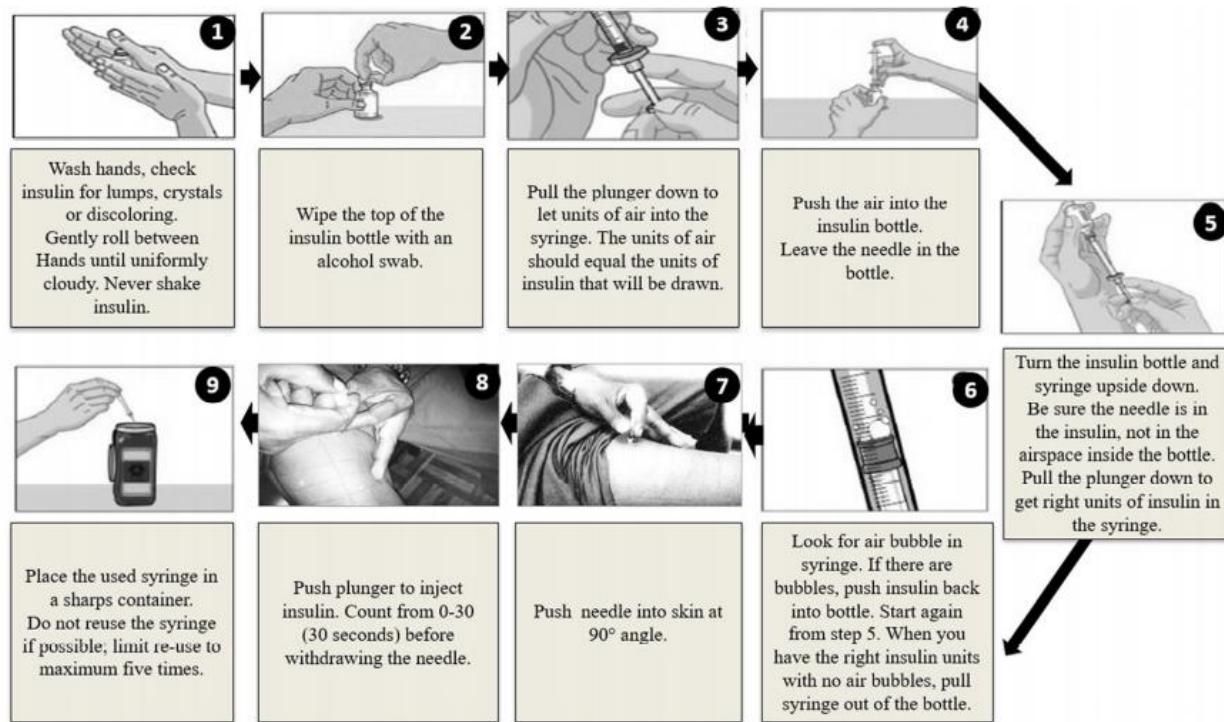


Figure 5 This figure shows the steps that should be taken when insulin is injected. (1) Hands should be cleaned, and insulin gently mixed if it is the cloudy insulin. (2) The rubber on the bottle should be cleaned with spirit. If spirit is not available, cleaning should be done with water and the rubber dried with a tissue. (3) Air equivalent to the volume of insulin to be drawn, should first be drawn into the syringe, then injected into the bottle containing insulin. This is done to avoid creating a vacuum in the bottle containing insulin. (5) Insulin as required is then drawn into the syringe. (6) Ensure that the correct position of tilting insulin downwards is done, so to avoid drawing insufficient insulin. Insufficient insulin will be drawn if the bottle is not tilted appropriately and the needle sticks above the insulin level. Air bubbles should be removed. (7) The needle is pushed into the skin at 90°. (8) The plunger is advanced down and injection completed. It is recommended to allow the insulin injected to stabilize under the skin, by counting from 0 to 30. (9) The needle and syringe is removed from the skin and discarded into a plastic container, for appropriate disposal as hazardous waste

Adapted from Bahendeka, S., Kaushik, R., Swai, A. B., Otieno, F., Bajaj, S., Kalra, S., ... & Karigire, C. (2019). EADSG guidelines: insulin storage and optimisation of injection technique in diabetes management. *Diabetes Therapy*, 10(2), 341-366.

Storage and Transportation

International Diabetic Federation categorized insulin as a 'cold chain product' because it loses potency when exposed to heat and when frozen. Storing and transporting insulin products within a temperature range of 2-8°C as long as it is unopened is needed to guarantee its full effectiveness.

Strict regulations and guidelines for the storage and transport of insulin have been imposed by the European Commission and World Health Organization (WHO). All parties involved such as manufacturers, distributors, doctors and pharmacists are obliged to ensure transport and storage at 2-8°C, with temperature monitoring and qualified refrigerators and shipping systems. Everyone ensures providing insulin to people with diabetes without destroying its potency.

Distribution from the manufacturer to pharmacy

- Maintain cold chain process within a recommended temperature range.
- In the event of a cold chain breach, insulin must be discarded.

Storage of Insulin at Health Care Facility

- Keep a refrigerator to store insulin.
- Do not store food, blood, or milk in this refrigerator.
- The refrigerator for insulin should be defrosted every 6–8 weeks if it is not self-defrosting.
- Keep an integral thermometer to monitor temperature ranges (This integral thermometer should be calibrated at least annually to ensure the readings are accurate)
- Store insulin in the refrigerator between 2 and 8 °C.
- Never place insulin in the freezer or directly on ice.

Transfer and storage of insulin from Pharmacy to Home/ People with diabetes

- When transferring insulin from health care facility, use an insulated bag or a cooling pouch to avoid sudden temperature variations if available.
- At home, store unopened insulin in an area of the refrigerator between 2 and 8 °C.
- Store insulin in current use (pen, cartridge or vial) at room temperature (20–25 °C), for a maximum of 6 weeks after initial use, and within the expiry date in a clean plastic box (**Figure 6**).
- Protect insulin from light.
- Do not expose insulin to temperatures above 32 °C or extreme cold sources (below 2 °C) because higher/lower temperatures will reduce its potency.
- Keep insulin out of reach of children.
- When transferring do not keep insulin in a locked car or in the glove compartment (Temperature in closed vehicles may reach very high levels (above 32 °C), with loss of potency of insulin).
- When travelling by air, carry insulin supplies, along with a prescription, in cabin baggage or handbag. Luggage which is checked-in is stored in the aircraft's hold and may freeze: any insulin in this luggage may lose its potency.

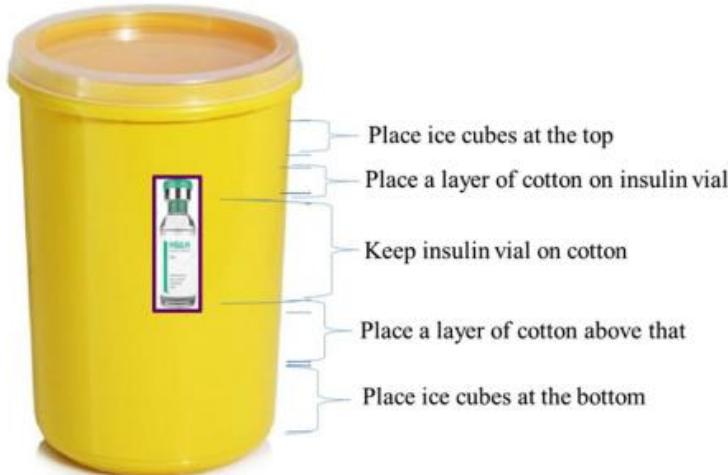


Figure 6 Figure showing a suggested improvised box for the transportation of insulin from the health facility or pharmacy to home. The ice will keep the temperatures favorable for transportation even in the heat of the sun. Furthermore, the cotton layers ensure that the melting ice will not spoil the labels on the insulin, and also act as cushions against undue shaking of insulin during transportation
Adapted from Bahendeka, S., Kaushik, R., Swai, A. B., Otieno, F., Bajaj, S., Kalra, S., ... & Karigire, C. (2019). EADSG guidelines: insulin storage and optimisation of injection technique in diabetes management. *Diabetes Therapy*, 10(2), 341-366.

Appendix 7

Recommended eating pattern for patients with diabetes

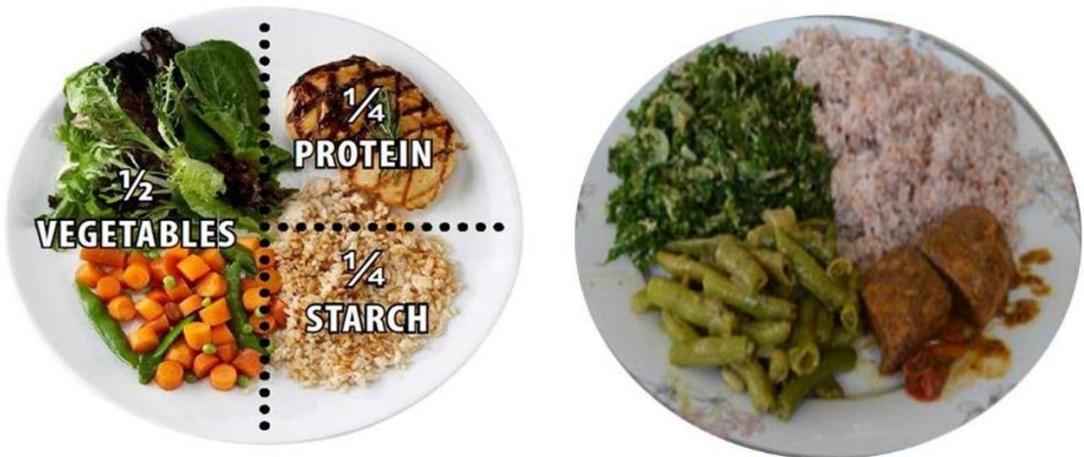
- Follows the plate method for main meals (at least for lunch and dinner).

Fill half your plate with non-starchy vegetables*. Fill a quarter of your plate with grains** or starchy vegetables***. Fill the remaining quarter with a healthy protein (fish, sea food, skinless chicken, eggs and pulses like dhal, cowpea, chickpeas, green gram or soy. Avoid processed meats like sausages and minimize red meats like beef, pork and mutton).

***Non-starchy vegetables:** green beans, cabbage, ladies finger (bandakka), gourd (pathola), wetakolu, murunga, brinjals (batu), cucumber, broccoli, carrot, pumpkin, ash plantains, beets, tomatoes and green leaves (mukunuwenna, kankun, gotukola, kathuru-murunga, saarana, spinach)

****Grains:** rice, wheat, kurakkan, maize, corn, rice or wheat flour preparations (bread, string hoppers, hoppers, pittu, roti). Examples of serving sizes of grains: rice: 1 to 1.5 tea-cups; bread: 2 to 3 slices

*****starchy vegetables:** tubers or yams (manioc, potato, sweet potato, innala, kiri ala), jackfruit and breadfruit



2. Boiled pulses (cowpea, chickpeas, green gram) alone can be consumed for breakfast as an alternative for the plate method (1.5 to 2 tea-cups)
3. Cooking techniques recommended: Steaming / boiling, stir-frying with a small amount of oil, cooking with water and spices, baking and consuming raw as salads. Avoid deep-frying and minimize coconut milk usage.
4. Eat fruits as snacks, i.e. 2-3 hours after a main meal. This will help to reduce the glycemic load of main meals and provide a healthy alternative for snacks. Serving sizes of fruits: one medium banana (4" length), one tea-cup of cut fruits.
5. Limit the intake of high-sugar, high-calories items such as sugar-sweetened beverages (sweetened tea/coffee, fizzy drinks), cake, biscuits, pudding, ice cream, chocolate, short-eats, mixture and take-out food.

Carbohydrate content in some commonly consumed food items

(Refer a carbohydrate counting book for details)

Food item	Portion size	Carbohydrate content (g)
Rice (white or red – boiled)	1 tea-cup (200ml)	30
Bread (sandwich)	1 slice	15
Noodles (boiled)	1 tea-cup (200ml)	18
Pol roti	3" diameter, 0.5 cm thick	24
Hopper	1	22
String hoppers (thin)	6	30
Potato (boiled)	Medium (egg sized)	10
Cowpea (boiled)	1 tea-cup (200ml)	25
Chickpeas (boiled)	1 tea-cup (200ml)	30
Green gram	1 tea-cup (200ml)	25

Banana	Medium (4" length)	15
Apple	Medium	15
Mango	Pieces – 1 tea-cup ful	15
Milk	200ml	10
Milk powder	3 full teaspoons (25g)	10
Yogurt (set)	1 cup	11

Common myths on diet

Myth	Scientific fact
Dates, jaggery and honey won't increase blood sugar, hence, are an alternative to sugar	Dates, jaggery and honey also contain sugar and will increase blood sugar
If I avoid sugar, I will not get diabetes	Several lifestyle factors increase diabetes risk: weight gain, unhealthy diet, sugary drinks, lack of exercise
I can eat whatever I want if I take medications to control diabetes	Healthy diet is an integral part of management of diabetes
If I control my diet, I can stop the medications for diabetes	Medications should not be discontinued without medical advice
Eating certain foods (e.g. Thebu, Kowakka leaves) will improve diabetes.	No single food item will improve blood glucose control
Kurakkan / atta flour are good for diabetes	Kurakkan and atta flour are grains similar to rice or wheat. They should be consumed similar to other grains
Consuming a 'light diet' like string hoppers is good for dinner	String hoppers belong to 'grains' food group. It is important to have vegetables and protein foods as part of a healthy meal, in addition to grains
Fruits contain sugar and therefore should be avoided	Fruits are an essential part of a healthy diet. Consume fruits as snacks in recommended quantities
"Diabetes-friendly", "sugar-free", "fat-free" foods are good for you	These foods may be high in calories. E.g. "sugar-free" products are generally high in fat
Canjee (Kurakkan, Kola kanda) is good for diabetes	Canjee mainly contains grains and coconut milk and hence is a high-carbohydrate, high-calorie food