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PAKISTAN ENDOCRINE SOCIETY (PES)

2023 GUIDELINES FOR MANAGEMENT OF TYPE 2 DIABETES MELLITUS AND CARDIOMETABOLIC SYNDROME

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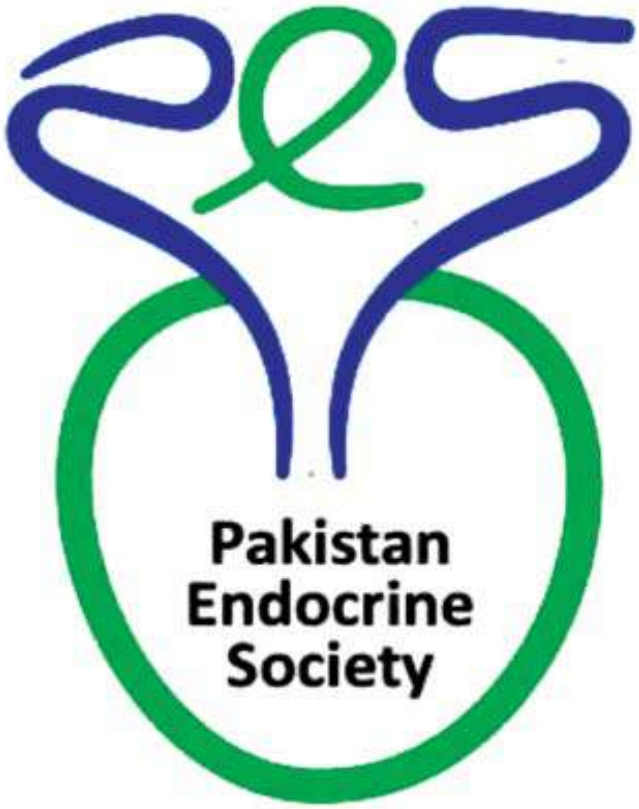
2023 GUIDELINES FOR MANAGEMENT OF TYPE 2 DIABETES MELLITUS AND CARDIOMETABOLIC SYNDROME



2023 Standards of Medical Care in
Diabetes & Cardiometabolic Syndrome

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President's Message

As the President of Pakistan Endocrine Society, I am pleased to share the third edition of the Guidelines for the management of Type 2 Diabetes Mellitus for the physicians involved in the delivery of diabetes care. As the Medical Education is progressing day by day so there is always the scope of new changes as per the updated knowledge about the management of diabetes and bringing such updates in our practice. These guidelines are designed on the basis of the approach to enable us to change our

practice according to the new updates. It will not only make our practice easy and simple but also will make us at par with international standards. Every effort has been taken to make these guidelines user friendly and easy to understand in a stepwise approach to the management of type 2 diabetes.

Pakistan Endocrine Society gives prime importance to the dissemination of knowledge and updating our fellow physicians to modify their practice according to the current international standards. I hope these guidelines will prove a major step in propagating the knowledge about diabetes care.

In the end, I would like to pay my special thanks to all the authors and reviewers whose efforts have given a practical form to these guidelines.

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PAKISTAN ENDOCRINE SOCIETY (PES) 2023
RECOMMENDATIONS FOR MANAGEMENT OF TYPE 2 DM

Definition: Diabetes is a complex metabolic disorder characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Type 2 diabetes is associated with multiple vascular risk factors and a wide range of complications; therefore, treatment is complex and time-consuming. Patient education and self-care are crucial parts of management. Comprehensive evaluation and management of diabetes can optimally be achieved through patient centred approach that requires a close working relationship between the patient and clinicians involved in planning treatment. Goal of treatment is to delay or prevent complications and to improve the quality of life. To achieve management goals various patient specific characteristics like current lifestyle, presence of comorbidities, degree of hyperglycaemia, weight/BMI as well as social and cultural aspects should be taken into consideration. Screening for complications of diabetes (microvascular and macrovascular) should be done at first visit and should be repeated at appropriate intervals, and depending upon the progression of disease. In patients with established diabetes, review previous treatment and risk factors. The 10-year risk of a first atherosclerotic cardiovascular disease (ASCVD) event should be assessed in all patients. Foot examination should be carried out and foot care advice should be given to all patients. Assessment of hypoglycaemia risk, modifications in lifestyle like alterations in dietary habits specially aiming to reduce weight in overweight or obese persons, increase in physical activity and smoking cessation are most important and initial steps in the management of type 2 Diabetes.

GUIDELINES FOR MANAGEMENT OF TYPE 2 DIABETES MELLITUS AND CARDIOMETABOLIC SYNDROME

Pakistan is currently third in the world in terms of prevalence of diabetes, with an estimated 33 million people affected per IDF data published in 2021.[1] Pakistan faces health challenges in diabetes due to its high prevalence and its related complications.[2]

Pakistan Endocrine Society (PES) guidelines for type 2 diabetes mellitus (T2DM) are based on most updated published evidence, and on local, regional and international guidelines, including considerations to affordability and availability of medicines in Pakistan. This is a consensus statement by Guidelines committee of PES.

These guidelines not only concentrate on diagnosis and management of T2DM but also provide a key to maintain the referral system from primary to secondary and tertiary care and vice versa. Special emphasis has been given to develop the concept of a multi-disciplinary team for the management of diabetes and hence chapters on nutrition, physical exercise and diabetes education have been included. The current document not only advocates glycaemic control to reduce microvascular and macrovascular complications including cardio-renal disease, but also highlights obesity as the underlying risk factor for the development of T2DM. In addition, the document emphasizes recommendations for blood pressure (BP) and lipid control, the two most important risk factors for atherosclerotic cardiovascular disease (ASCVD) in addition to comprehensively managing micro and macro vascular complications. These recommendations will be revised periodically. Any major changes in the intervening period will be included as addendum/corrigendum.

It is important to highlight that these are only guidelines and hence individualized approach according to specific scenario is still the key to the management.

Introduction

Pakistan Endocrine Society (PES) guidelines for type 2 diabetes mellitus (T2DM) are based on available local, regional and international scientific evidence including special considerations to affordability and availability of medicines in Pakistan and consensus statements by Guidelines committee of PES.

PES has made following recommendations on different issues pertaining to T2DM for Pakistan

RECOMMENDATIONS

RECOMMENDATION - 1: Risk of Developing T2DM

1.1- High risk individuals are advised for laboratory testing. People with a positive screening test should proceed to a diagnostic test as described in section 2. If the result of that test is normal, they should be advised on healthy lifestyle changes and the diagnostic test should be repeated every year

RECOMMENDATION-2: Screening and Diagnosis of T2DM

2.1- Diabetes can be diagnosed on the basis of any of the following criteria:

a Fasting plasma glucose: ≥ 126 mg/dl (≥ 7.0 mmol/L) - Fasting defined as no caloric intake for minimal 8 hours, or.

b. Plasma glucose: ≥ 200 mg/dl (11.1 mmol/L) in the presence of symptoms.

c. OGTT is cumbersome, not reproducible and used only now in pregnancy

d. HBA1c value of ≥ 6.5 DCCT (Diabetes control and complication trial) aligned and NGSP (National Glycohemoglobin Standardization Programme) certified Unless unequivocal symptomatic hyperglycaemia is present, the diagnosis should be confirmed by repeat testing on a different day.

Diagnostic Criteria [3, 4].

	Normal (mg/dl)	IFG/IGT (MG/DL)	Diabetic (mg/dl)
FBG	<100	100-125	> 126
RBG/75gm OGTT	< 140	140-199	> 200
HBA1C	< 5.7	5.7-6.4	> 6.5

FBG-Fasting Blood Glucose IFG: Impaired Fasting Glucose IGT-Impaired Glucose Tolerance

2.3- The above-mentioned tests should be performed in the laboratory..

2.4- Asymptomatic individuals with a single abnormal test should have the same test repeated to confirm the diagnosis. On the other hand, if a patient has discordant results in two tests, the test result that is above the diagnostic cut point should be repeated.

Symptomatic individuals do not need repetition of the abnormal test.

RECOMMENDATION - 3: Glycaemic Targets & Assessment of Glycaemic targets

Recommendation No 3.1: Glycaemic Targets:[6]

Sub Category	Fasting Blood Glucose FBG mg/dl	Random Blood Glucose RBG mg/dl	Bed time Blood Glucose	HbA1c%
Recent/without complications	80-120	80-160	100-140	6.5-7%
With CCF*, CKD, CLD Autonomic Neuropathy	100-140	120-180	120-180	7.0-7.5%

CCF= Congestive Cardiac Failure CKD-Chronic Kidney Disease CLD- Chronic Liver Disease

Recommendation - 3.2: Assessment of Glycaemic targets:

Recommendation for those with co-morbidities and if duration of diabetes greater than 10 years is 7.5%, they may be further increased in elderly and frail patients is 8.5%.

Recommendation - 3.2.1: HbA1c:

Perform the HbA1C test at least two times a year in patients who have stable glycaemic control.

Perform the HbA1C test quarterly in patients whose therapy has changed or who are not meeting the glycaemic goals.

For most non-pregnant T2DM patients a reasonable HbA1C goal is < 7%.

For selected individual patients (short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease) HbA1C goal such as 6.5%, may be advised if this can be achieved without significant hypoglycaemia.

Less stringent A1C goals such as, 8% may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or longstanding diabetes.

Recommended- 3.2.2: Self-monitoring of blood glucose (SMBG):

Frequency of SMBG will vary according to the treatment regimen and affordability of patients. Adherence to the prescribed frequency should be emphasised whenever possible.

Diagnostic Criteria.[3, 4]

1. Daily SMBG is superior to less frequent monitoring.

2. After achieving target blood glucose SMBG can be done less frequently.

3. Monitoring BG before going to bed at night should be done to prevent nocturnal hypoglycaemia.

1. Low Intensity SMBG: Two times/week (pre breakfast + bedtime), for most controlled non-affording T2DM and geriatric patients (age > 70 years) controlled with or without co-morbid conditions.

2. Moderate Intensity SMBG: Two times daily (pre breakfast + one post meals can be suggested), for newly diagnosed or un-controlled non-affording T2DM and controlled affording T2DM plus geriatric patients.

3. High Intensity SMBG: SMBG can be done 4 to 5 times every day or on alternate days until target blood glucose is achieved. Once target is achieved, SMBG can be done 3 times (pre breakfast and Pre- and Post-meal of major meal or other meals as required every 4th or 5th day or as required).

4. Intensive Intensity SMBG: For pregnant women on MNT or on metformin a total of 14 readings per week including pre-breakfast and 1h PPG or 2h PPG are suggested.

Recommendation 4: Non pharmacological Management of Diabetes

Recommendation 4.1: Lifestyle modifications (LSM):

The key components of lifestyle therapy include:

1. Diabetes self-management education (DSME)

2. Medical nutrition therapy (MNT) comprising of patterns on healthy diet,

3. Regular and adequate physical activity, sufficient amount of sleep,

4. Smoking cessation with avoidance of all tobacco products

Lifestyle modification in new onset diabetes can lead to diabetes remission. Remission is defined as a return of HbA1c to less than 6.5% that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose lowering pharmacotherapy.

We have evidence of Diabetes remission in Type 2 Diabetes from Direct study conducted in UK.[12]

Men and women between 20-65 years, BMI 27–45kg/m^2, T2DM diagnosed within 6 years, HbA1c ≥6.5 should be shifted on a low calorie 800KCAL diet with full diet replacement. It can push diabetes in remission. Weight loss of 10 to 15 kg achieved by using low caloric formula diet (825 – 853 kcal) for 12 to 20 weeks followed by gradual reintroduction of food and maintenance of weight loss led to remission of diabetes in patients with type 2 diabetes and BMI 27-45 kg/m2.[12]

Recommendation 4.1.1: Diabetes self-management education:

Persons with T2D must improve their lifestyle from the time of diagnosis to reach the metabolic targets as soon as possible. This can be achieved best assisted with an effective education programme

- Patients with T2D should be referred to a diabetes education programme at the time of diagnosis and the programme should be conducted by a trained diabetes educator (where available).
- Set individualized target glycated haemoglobin (HbA1c) levels with the patient, and provide a level of care to achieve and maintain that target.
- Offer self-monitoring of blood glucose as an integral part of self-management, and agree when it should be performed and how it should be interpreted and acted upon. A glucometer with low CV (coefficient of variance) can be a reliable tool to be used.
- When starting insulin therapy, employ a structured training programme with active dose titration.

Recommendation 4.1.2: Medical Nutrition Therapy (MNT):[8-11]

MNT should be started soon after diagnosis of T2DM by someone with training in nutrition therapy preferably by a registered dietitian (where available) and reviewed as per need.

- MNT should be aimed at achieving normoglycaemia and providing adequate calorie intake.
- Simple sugars should be avoided. Food containing complex carbohydrate intake is recommended.
- High dietary fibre and whole grain containing foods should be encouraged.
- Lean protein, oily fish and vegetable consumption should be increased.
- Provide personalized diet plan in the form of printed diet charts while plate models can be used where necessary.

Recommendation 4.1.3: Regular and adequate physical activity: [12-14]

- Physical Activity (PA) is an effective intervention in improving glycaemic control, blood pressure and lipid levels in addition to improving sense of well-being.
- If patient has not been active at all, start slowly and increase activity over a period of time. Simple walk for at least 30 minutes per day, 5 days a week is enough in initial phases or simple aerobics that increase heart rate to 60-70% of maximum (Maximum Heart Rate = 220 - age in years).
- Minimal but significant changes in lifestyle like using stairs instead of taking elevators, parking car at a distance from workplace, keep walking while having conversation on phone etc. can bring significant change in activity status of a person.
- Plenty of water should be taken to avoid dehydration. In extremes of weather, indoor alternative exercises are favoured.
- Strengthening exercise to improve muscle mass has also been mentioned.

Recommendation 4.1.4: Adequate Sleep: 14, 15

- All patients should be advised to sleep on average approximately 6-7 hours every night.
- Six to 9 hours of sleep every night is associated with a reduction in cardiometabolic risk factors, whereas sleep deprivation aggravates insulin resistance, hypertension, hyperglycaemia, and dyslipidaemia and increases inflammatory cytokines.

Recommendation 4.1.5: Smoking Cessation:

- Smoking cessation is another important component of lifestyle therapy and involves avoidance of all tobacco products including pan, gutka, huqqa, niswar, shisha and e-cigarettes.

- It should be emphasized that smoking is associated with an increase in cardiometabolic risk factors including insulin resistance, hypertension, hyperglycaemia, and dyslipidaemia.
- Counselling to quit smoking should be done at each visit.

Recommendation 4.1.6: Weight Reduction:[16,17]

- For weight reduction emphasis should be placed on lowering caloric intake and inducing weight loss for patients with type 2 diabetes who are overweight.
- A sustained weight loss of even 5 to 10 percent of initial body weight in overweight individuals can have a lasting beneficial impact on serum glucose, dyslipidaemia, and hypertension.
- Physical activity, diet, and behavioural modification are important components to accomplish weight loss. As mentioned earlier with reference to DiRECT study, low calorie 800 kcal diet with full diet replacement can be helpful in remission of diabetes ([12]).

Options for weight loss are medications and bariatric surgery. In obese type 2 diabetics preferable medicines will be like SGLT-2 I and GLP-1, including upcoming weight loss medications like liraglutide, semaglutide and Tirzepatide.

Recommendation 5: Pharmacological Management of Diabetes 18-20

- Pharmacological therapy should be considered if one fails to achieve glycaemic targets with nonpharmacological therapy (MNT & Physical activity) within target days. This should not be more than one month provided blood glucose is monitored and not significantly elevated.
- Pharmacological treatment should be started right away if significant hyperglycaemia is documented at time of diagnosis.
- The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves in addition to the patient's cardiac, cerebrovascular, and renal status.
- The choice of therapy also considers ease of use and affordability. The therapeutic regimen should be as simple as possible to optimize adherence.
- Any of the selected regimes should be evaluated every three months with HbA1c and SMBG.
- Visit could be scheduled at shorter interval if there is glycaemic variability or hyper/hypoglycaemia anticipated in initial management.
- If HbA1c is not available, SMBG and/or lab records can be helpful.
- People with diabetes should be assessed for possible side effects of drugs including hypoglycaemic events, weight gain, fluid retentions, hepatic or renal impairment or cardiovascular risks.
- They should also be assessed for co morbidities, drug adherence and psychosocial issues.

Recommendation 5.1: Initial monotherapy

- First-line therapy depends on comorbidities, patient-centred treatment factors and management needs and generally includes metformin and comprehensive lifestyle modification
- Other medications (glucagon like peptide 1 receptor agonists, sodium – glucose co transporter 2 inhibitors), with or without metformin based on glycaemic needs, are appropriate initial therapy for individuals with type 2 diabetes at high risk for atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease.
- Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycaemic and metabolic benefits.

Recommendation 5.2: Initial Combination Therapy:

- In newly diagnosed people with diabetes presenting with signs and symptoms of hyperglycaemia or having HbA1c >8.5%, a second oral agent or insulin should be considered along with metformin. Initial combination of submaximal doses of antihyperglycaemic agents produces better and quicker response than maximum doses of monotherapy.
- Starting with dual combination therapy is optimal in south east Asian population with higher HbA1C,

especially in the presence of ASCVD risk factors (microalbuminuria, young age, eGFR<60 ml/min/1.73 m2) as it achieves early glycaemic control and overcomes therapeutic inertia[13].

Recommendation 5.3: Initial Insulin Therapy:

- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/ or have A1C ≥ 10% (86 mmol/L) and/or blood glucose levels ≥ 300 mg/dL and if there is evidence of ongoing catabolism (weight loss).[18-20]
- Insulin as initial therapy is recommended for treatment of T2DM in people who are unable to tolerate oral hypoglycaemics or non-insulin injectables, in situation when there is suspicion of patient having Type 1 vs. 2 and confirmation is not possible, being treated for acute complications of diabetes (DKA, HHS), undergoing surgery, unable to use oral hypoglycaemics and non-insulin injectable due to allergies, renal or hepatic disorders in newly diagnosed patients with signs and symptoms of ketosis.
- Insulin can be categorized according to either duration of action ranging from rapid acting insulin to short acting, intermediate acting, long acting and very long-acting insulin or their source as human or analogue insulin. The human insulin is less expensive than analogues, hence more affordable.
- The dose should be adjusted at regular intervals. Less expensive human insulin is beneficial in most of the cases particularly if comprehensive education about preventing; identifying and timely correction of hypoglycaemia has been imparted.
- Required initial dose is 0.2 to 0.5 U/kg/day or 10 U/day. Obese people may need higher dose. Treatment should be graded to reach the targets and avoid unnecessary risk to patient (hypoglycaemia). General rule is to start low and go slow if possible, in titration of Insulin.

Recommended approach to start insulin:

Step 1: In case of high fasting blood glucose (FBG), an intermediate acting human insulin or basal analogue insulin with a dose of 0.1 to 0.2U/kg or 10 U/day can be added at bedtime with the current oral therapy. The insulin dose may be titrated once or twice/week to reach the desired FBG. Analogue basal (Ultra long acting) insulin can be given at fixed time of the day to have proper effect on fasting blood glucose.

Step 2: High post meal blood glucose should be controlled by bolus insulin, either by regular human insulin or by ultra-short acting insulin analogue with meal(s) and titrated every 48 to 72 hours to achieve the desired post-meal targets.

- Initial use of pre-mixed insulin regimens should ideally be avoided as it may not achieve the desired targets and put the patient at risk of fluctuating glycaemic control. However, premixed insulin can be considered on individual basis where patients are unwilling to or unable to take basal bolus regimen. Insulin regimens like free mixing can also be considered for better management. These regimens require a vigilant follow up and patient's understanding of insulin use.
- Add GLP-1 receptor agonist to the basal insulin. The combination of GLP-1 receptor agonist and basal insulin is more effective in lowering glucose levels and has a lesser chance of weight gain and hypoglycaemia as compared to the intensified insulin regimen and also provides additional cardiovascular benefits to patient. However, cost is a major challenge in poor socioeconomic population.

Step 3: Intensive Insulin Therapy:

- If the HbA1c target is still not being met on basal insulin along with single injection of rapid-acting insulin before the largest meal of the day, proceed to a basal-bolus regimen with either 2 or 3 injections of rapid-acting insulin before each meal i.e. before breakfast, lunch and dinner. Insulin regimens like split mix and modified split mix can also be considered for better management. These regimens require a vigilant follow up and patient awareness about risk of hyper/hypoglycaemia. These regimens require very intensive patient education.

Recommendation 6: Hypertension and Diabetes

High blood pressure is recognized as a major risk factor for CVD and CKD.

Recommendation 6.1: Monitoring of Blood pressure:

Recommendation 6.1.1: Blood pressure should be measured at every clinic visit. Patients newly diagnosed with systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg should have blood pressure reading multiple times and confirmed on a subsequent day. Patients with history cardiovascular disease and blood pressure reading of ≥180/110 mmHg; a single visit is sufficient to diagnose hypertension.

Recommendation 6.1.2: Domiciliary or 24 hours Ambulatory Blood pressure monitoring is advised for all patients with Hypertension. On the initial visit orthostatic blood pressure should be checked and may be repeated as indicated.

Recommendation 6.1.3: Blood pressure measurement should be measured by trained personnel. Standard protocol for blood pressure measurement must be followed i.e., in the seated position, with feet on the floor and arm supported at heart level, after 5min of rest. Cuff size should be appropriate for the upper arm circumference.

Recommendation 6.2: Blood Pressure Targets:

Recommendation 6.2.1: For patients with hypertension and type 2 diabetes, blood pressure targets should be individualized keeping in mind the potential side effects of drugs, patient preferences and cardiovascular risks.

Recommendation 6.2.2: For individuals who have hypertension but no other co- morbidities, blood pressure target should be less than 140/90. For individuals with pre-existing ASCVD, target BP of less than 130/80 would be more appropriate if it could be achieved safely. In pregnancy with pre-existing hypertension, a BP target of 110–135/85 mmHg is suggested.

Recommendation 6.3: Therapeutic Management Strategies

Recommendation 6.3.1: For those patients with BP of more than 120/80 mmHg, Lifestyle intervention should be started in the form of weight loss if required, increase in physical activity, moderation in alcohol intake, reduction in sodium intake to less than 2300 mg per day, increase in consumption of vegetables and fruits, low fat dairy product.

Recommendation 6.3.2: Patients with confirmed blood pressure readings of >140/90mmHg should be promptly initiated pharmacological therapy; in addition to dietary changes Therapy must be titrated to achieve the desired goals.

Recommendation 6.3.3: Patients with confirmed blood pressure readings of ≥160/100 mmHg should be promptly initiated and timely titrated two drugs or a single-pill combination of drugs.

Recommendation 6.3.4: For hypertensive patients with type 2 diabetes, ACE inhibitor/ARBs should be considered as initial therapy.

If target blood pressure level is not achieved after 2-3 months, addition of either a dihydropyridine calcium channel blocker or thiazide diuretic may be considered. (NICE AND ADA GUIDELINES)

β-Blockers have not shown any reduction in mortality as antihypertensive agent in absence of active angina, history of MI or HfrEF.

Recommendation 6.3.5: ACE inhibitors or angiotensin receptor blockers are also recommended in patients with diabetes and hypertension with urinary albumin to creatinine ratio ≥300 mg/g creatinine and suggested when it is between 30–299 mg/g creatinine.

Recommendation 6.3.6: A blood pressure ≥140/90 mmHg despite of lifestyle modifications plus optimal doses of three antihypertensive drugs including a diuretic is labelled as 'Resistant hypertension'.

Recommendation 6.3.7: Mineralocorticoid receptor antagonists have shown to be effective while managing resistant hypertension in patients with diabetes when they are added to existing treatment regimens.

Recommendation 6.3.8: Safe antihypertensive drugs in pregnancy include methyldopa, nifedipine (long acting preparation) and labetalol while hydralazine can be considered in settings where rapid control of blood pressure is required in pregnancy or in severe preeclampsia.

Recommendation - 7: Dyslipidaemia and Diabetes:

High blood lipid levels are considered as a major cardiovascular risk factor and particularly high LDL cholesterol. All people with T2D and established CVD should start treatment with a statin (secondary

prevention).

Recommendation 7.1: Perform lipid profile including total cholesterol (TC), Low density Lipoprotein cholesterol (LDL-C), High density Lipoprotein Cholesterol (HDL-C) and Triglycerides (TG) at the time of diagnosis.

Recommendation 7.2: Lifestyle modifications specially targeting weight reduction in overweight or obese people and modification of diet is the important part of management of dyslipidaemia.

Recommendation 7.3: For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy.

Recommendation 7.4: For patients with diabetes aged 20–39 years (might be risk in women of child bearing age) with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy.

Recommendation 7.5: In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy.

Recommendation 7.6: If statin is not tolerated or a particular LDL-C goal is not achieved on statin alone, addition of a non-statin lipid-lowering agent can be considered. If LDL cholesterol is >70 mg/dL on maximally tolerated statin dose in patients with diabetes and atherosclerotic cardiovascular disease, consider adding additional LDL lowering therapy (such as ezetimibe).If LDL target is not achieved on addition of ezetimibe to statin we can add other available agents are PCSK 9 inhibitors, Inclisaran, Bempedoic acid.

Recommendation 7.7: If triglycerides are high, more than 150mg/dl but less than 500mg/dl, strict lifestyle modifications, glycaemic control and statins are recommended.

Recommendation 7.8: If triglycerides are >500 to 1000 mg/dL (5.7-11.4 mmol/L) despite lifestyle changes and improved glycaemic control, should start a fibrate to prevent acute pancreatitis.

Recommendation 7.9: When a health care provider considers that the patient needs statin therapy, it should be maintained lifelong.

Recommendation - 8: Antiplatelet Treatment

Recommendation 8.1: Role of aspirin in primary prevention is debated

Recommendation 8.2: Aspirin should be given to all patients with established CVD disease. (Secondary prevention)

Recommendation 8.3: It may not be recommended in people younger than 50 years without additional CVD risk factors.

Recommendation 8.4: People intolerant to aspirin or if there is any contraindication, Clopidogrel is an alternate option.

Recommendation 8.5: Aspirin can be prescribed at a dose of 75-162 mg/day for both primary (high risk) and secondary prevention where indicated.

Recommendation 8.6: Dual antiplatelet therapy (aspirin plus clopidogrel) is not indicated for primary prevention in T2DM.

Recommendation 9: Screening for Microvascular Complications:

Recommendations 9.1: Retinopathy screening

- All patients of type 2 diabetes should have dilated eye examination by an ophthalmologist at diagnosis or at first visit to the clinic.
- If the screening for retinopathy is positive or if the patient has unexplained reduced visual acuity with or without retinopathy, the individual should be referred to an ophthalmologist.
- If no sign of retinopathy is present repeat examination annually or every other year. If retinopathy is present, frequency of examination should be suggested by ophthalmologist.
- Aspirin can be safely prescribed in patients with retinopathy as it does not increase the chances of retinal haemorrhage unless there is some other contraindication.
- ≥30 mg/g creatinine

Persistent albuminuria requires treatment with an ACEI

Recommendations 9.2: Nephropathy screening

- All patients with type 2 diabetes should be

screened for microalbuminuria annually.

- Measure serum creatinine every six months to calculate eGFR, once albuminuria is detected and/or when other risk factors are present (e.g., hypertension).
- Uncontrolled diabetes or hypertension, fever, infection, recent exercise or congestive cardiac failure may result in proteinuria without kidney disease.
- Two readings three months apart should be taken before making a diagnosis of nephropathy.
- Diabetic kidney disease (DKD, diabetic nephropathy) is identified when eGFR is <60 mL/min/1.73 m2 and/or albuminuria ≥30 mg/g creatinine.
- For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium-glucose cotransporter2 inhibitor which has shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both.
- In non-pregnant patients with diabetes and hypertension the first line antihypertensive are ACEI or ARBs. Combination of these drugs with each other's should be avoided due to increased incidence of hyperkalaemia.
- In selected high-risk patients, serum creatinine and potassium should be rechecked after 10 days and 6 weeks in cases of newly prescribed ACEI/ARBs. It is common to have an acute rise in serum creatinine of up to 30% within 2-5 days of initiating an ACEI/ARB. These can be safely continued in patients if the creatinine subsequently stabilizes at the higher level.
- Good metabolic control is essential to delay the progression of nephropathy.
- People should be referred to a nephrologist when they have DKD stage 4 or 5 (eGFR<30 mL/min/1.73 m^2) or unexplained heavy proteinuria with or without haematuria in the absence of retinopathy or with short disease duration (e.g., other causes of renal disease) or with a rapid fall in the eGFR.

Recommendation 9.3: Neuropathy screening

- All people with diabetes require thorough assessment for peripheral neuropathy on presentation. Frequency of follow up assessment depends on presence of neuropathy and/or loss of protective sensations.
- Most common presenting complaints are pain, burning and tingling sensations. Almost 50% of patients may be asymptomatic. Identifying these insensate feet is important for prevention of foot ulcers.
- This assessment includes testing with 10 grams monofilament and any of the additional tests for pin prick, vibration or temperature sense to identify if the foot is at risk.
- Medications with proven efficiency include duloxetine, gabapentin or pregabalin can be given as initial treatment. Additionally amitriptyline and nortriptyline can be offered with caution due to side effect profile.
- Other Secondary causes of Neuropathy must be evaluated in case of new onset neuropathy. In patients presenting with atypical or painful neuropathy, other causes should be excluded like, vitamin B12 deficiency, renal disease, Vasculitis, thyroid disease, vitamin D Deficiency, neurotoxic medications, chronic inflammatory demyelinating neuropathy etc., by obtaining relevant tests.
- History should be enquired regarding symptoms of autonomic neuropathy involving cardiovascular system, gastrointestinal tract including gastroparesis, genitourinary system including erectile dysfunction (ED) and offer appropriate treatment.

Recommendations 10: Screening for Macrovascular Disease

Recommendations 10.1: Screening for Coronary Artery Disease:

- Screen for coronary artery disease (CAD) when the patient has typical or atypical symptoms (Chest pain, shortness of breath, orthopnoea, paroxysmal nocturnal dyspnoea etc.)
- Assess cardiovascular risk factors in all T2DM patients annually (Hypertension, dyslipidaemia, smoking, obesity, family history of premature CVD etc.). Special attention should be paid to patients presenting with microvascular complications such as retinopathy / microalbuminuria as they might have silent macrovascular complications well.
- Offer aspirin and statin to patients who are at increased risk of CVD.

- Offer ACE inhibitors or ARBS to hypertensive diabetic patients with nephropathy.
- TZDs should be avoided in symptomatic patients with CHF

Recommendations 10.2: Screening for Peripheral Artery Disease (PAD):

- Screen for peripheral artery disease (PAD) by palpating the foot pulses and/ or measuring the SBP to calculate the ankle/brachial index.
- If symptoms of peripheral arterial disease are present refer the patient to secondary/tertiary care.
- All diabetic patients with non- healing ulcer having ABI <0.9 should be referred to secondary or tertiary centres for further evaluation of PAD by colour duplex ultrasound followed by CT angiography, MR angiography or standard X ray angiography, if required.
- All patients with diabetes and an ischaemic foot ulcer should receive aggressive cardiovascular risk management including support for cessation of smoking, treatment of hypertension, control of hyperglycaemia and prescription of a statin as well as low-dose aspirin or clopidogrel.
- Consider re-evaluating the Diabetes regimen in these individual. SGLT 2 Inhibitors use should be assessed as they have potential of complication like amputation when used in patient with PVD.

Recommendation 11: Diabetes and Foot Care:

- Examine feet at each clinic visit to identify the presence of peripheral neuropathy, peripheral artery disease, previous healed ulcers, foot deformity, signs, improper hygiene or foot wear.
- History of claudication or rest pain in lower limb should be taken. Inspect for colour, temperature or oedema. Palpation of peripheral pulses at each examination should be done.
- A risk category should be assigned (Table-1) for further preventive measures. Examination is also essential even in the absence of symptoms.
- Assessment of neuropathy can be done with 10 gm. Monofilament for pressure perception, 128 Hz tuning fork for vibration sense and tactile sensation by cotton wool. Achilles tendon reflex should be examined.
- People should be referred to a vascular surgeon if they have severe intermittent claudication.
- Persons with diabetic foot ulcers should be referred to a diabetic foot clinic, where the treatment by a multidisciplinary specialized team will reduce the risk of amputation and the time to functional recovery.

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CHAPTER NO.1

Referral criteria for diabetic patients in specialist clinic

1.1 : Primary Care physician is the first level of contact for individuals, families and communities, with the health care system. Primary health care facility for people with diabetes shall preferably be offered by certified diabetes doctors and educators. Diabetes educators are an essential part of primary care level.

1. Proper record maintenance for all people with diabetes attending the primary care clinic is advisable.
2. Screening for complications of diabetes should be done at first visit if facilities are available and should be repeated at appropriate intervals, and depending upon the progression of disease (details mentioned below).
3. A urine detailed report test should be performed. If proteinuria is present, other causes of proteinuria like urinary tract infection, renal calculi, recent fever or exercise etc. should be excluded. The test should be repeated within three months. If it is negative for proteins, test for urinary microalbuminuria is recommended if available or referral is appropriate. In case of presence of microalbuminuria, referral should be made to secondary care for further evaluation.
4. If serum creatinine level is ≥ 1.5mg/dl, referral to secondary care should be considered for further evaluation.
5. The patient should be referred to an ophthalmologist for visual acuity and comprehensive eye examination on the first visit and at least annually thereafter.
6. Foot examination should be carried out and foot care advice should be given to all patients (see chapter 8).
7. Patients presenting with "Feet at Risk" and/or diabetic foot ulcers should be referred for management and/or evaluation.
8. Acutely swollen painful and/or hot limb /limbs need urgent referral.
9. Diabetic patients with other chronic illnesses like tuberculosis, leprosy, hepatitis B or C, cardiovascular disease and secondary hypertension etc., should be referred to secondary / tertiary care for comprehensive management.
10. If there is recurrent significant hypoglycaemia, the patient should be referred to secondary care level for thorough assessment.
11. Patients presenting with sudden onset of limb weakness or painful neuropathy unresponsive to first line therapy or patients having signs and symptoms of autonomic neuropathy should be referred.
12. Primary care physicians (PCP) should refer the following patients to an endocrinologist or diabetologist or district medical specialist: those with poor metabolic control or having multiple co-morbidities and/or need complex treatment (such as those who need more than three glucose lowering drugs including basal insulin) and/or need resetting of the target for glucose control.
13. PCPs should also refer people with atypical presentation of diabetes such as young onset T2DM with strong family history (MODY?), rapid failure with oral glucose lowering drugs (LADA?) or atypical features suggestive of another endocrinopathy (e.g., Cushing's syndrome, Conn's syndrome, pheochromocytoma and acromegaly).
14. All Type 1 diabetic patients
15. Poor Glycaemic Control with HbA1C >8%.
16. Patients for initiation of insulin where expertise does not currently exist in primary care setting
17. Predominantly patients already on insulin, who require more appropriate insulin regimes
18. Recurrent Hypoglycaemia
19. For initiation of GLP1 analogue if patient meets the criteria.
20. All women with diabetes to be referred before stopping contraception or urgently at the point they become pregnant
21. Management of Gestational Diabetes Mellitus

22. People with Type 2 diabetes with BMI > 35 on maximum oral therapy/insulin who are motivated and capable to lose weight.
23. Patients with medical problems: where they affect diabetes control, such as those requiring steroids, organ transplantation or undergoing chemotherapy
24. Patients with known or suspected types of secondary diabetes that require specialist treatment
25. Patients where there is diagnostic uncertainty
26. Patients with Dyslipidaemias
27. New development of microvascular complications+

- Nephropathy = CKD 3B - 5
- Retinopathy requiring ophthalmology follow up
- Neuropathy: mononeuritis, amyotrophy, painful neuropathy if not responding to first- line treatment
- Autonomic neuropathy e.g., gastroparesis

28. Broadly, infected or non-healing ulcers, painful neuropathy, Charcot, requirement for foot care or ulceration with vascular disease
29. Any recent admission with acute diabetes complications e.g., DKA, HONK
30. Continuous glucose monitoring or insulin pump assessment in Type 1 Diabetes
31. Vocational drivers on insulin or medication that can cause hypoglycaemia
32. Patients with diabetes and erectile dysfunction in whom oral phosphodiesterase inhibitors are ineffective or contra-indicated (for example, patients on nitrates) [1,2]

1.2: Secondary Care

1. The secondary care comprises of multidisciplinary team supervised by a physician having postgraduate qualification or specialized training in diabetes care. The team includes qualified diabetes educators and diabetic foot care assistants.
2. Proper record maintenance of all people with diabetes attending the secondary care clinic is advisable (ideally electronic).
3. For initial assessment of proteinuria, protocol discussed in primary care level should be followed. Patients with positive dipstick test (1+ or greater) proteinuria should be confirmed by a quantitative measurement (protein- to creatinine ratio or albumin-to-creatinine ratio) within 3 months.

   Patients with two or more positive quantitative tests temporally spaced by 1 to 2 weeks should be diagnosed as having persistent proteinuria and undergo further evaluation and management for chronic kidney disease. These patients should be referred to tertiary care centres.
4. The patients should be referred for a comprehensive eye examination by an ophthalmologist on the first visit, and annually thereafter or according to the advice of the ophthalmologist. An eye emergency should be referred to ophthalmologist immediately.
5. Comprehensive foot examination should be carried out on first visit. Foot care advice should be given to all patients. Identified "Feet at Risk" or patients presenting with foot ulcers should have prompt management. Ulcers not responding to extensive management or showing signs of deterioration at any stage and patients needing vascular surgery or amputation should be referred to a specialized tertiary care foot care clinic.
6. An ECG should be performed in all patients and referral to tertiary care shall be considered if significant changes are present.
7. Patients with other chronic illnesses like tuberculosis, leprosy, hepatitis B or C, heart failure, ischaemic heart disease or angina and secondary hypertension etc., should be directed towards tertiary care if comprehensive management for these conditions is not available at secondary level.

1.3 Tertiary Care Tertiary care level

Tertiary Care Tertiary care level is a university-based teaching hospital comprising of an outpatient and inpatient integrated care along with research and education programmes. Routine integrated care involves the patient, physician (Professor, Associate Professor, Assistant Professor) with special interest in diabetes, clinical nurse specialist/educator trained in diabetes, dietitians, diabetic foot care assistants and/or podiatrists.

Ideally this setup should have necessary disciplines available such as, cardiology, nephrology, ophthalmology, dentistry, psychiatry, orthopaedic surgery, vascular surgery, gynaecology and obstetrics etc., providing care for all aspects of diabetes and its complications from prevention to rehabilitation. Any condition that requires more specific intervention should be directed towards more specialized centres.

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CHAPTER 2

Diagnosis, screening and monitoring of diabetes mellitus

Recommendation-1
Risk of Developing T2DM

1.1- Pakistan ranks 3rd in the world with an estimated prevalence of 33.0 million people with diabetes as per IDF data published in 2021.[1]

1.2- Population based screening for diabetes may be done using a locally validated screening test such as the Risk Assessment of Pakistani Individuals for Diabetes (RAPID) scoring system.2 (Risk score attached). High risk individuals are advised for laboratory testing. People with a positive screening test should proceed to a diagnostic test as described in section 2. If the result of that test is normal, they should be advised on healthy lifestyle changes and the diagnostic test should be repeated every year. [2]

Recommendation-2

- Diabetes can be diagnosed by using value of fasting plasma glucose (FPG), 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or A1C criteria.[2]
- FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic screening. It should be noted that the screening tests do not necessarily detect diabetes in the same individuals.
- Primary interventions are effective only in individuals with impaired glucose tolerance with or without impaired fasting or HbA1C.[3]
- Tests are same for screening and diagnosis.
- There may be discordance between the fasting plasma glucose, 2-h PG and HbA1C. The 2-h PG value more accurately diagnoses diabetes and prediabetes.[4]
- When there is discordance between A1C +values and glucose values, FPG and 2-h PG should be used for diagnosis. [5]
- The A1C test with a diagnostic threshold of >6.5% diagnoses only 30% of the diabetes cases identified collectively using A1C, FPG, or 2-h PG, according to National Health and Nutrition Examination Survey (NHANES) data.[6] so, should not be used as a sole diagnostic test for diabetes diagnosis.
- Diagnosis can be made on single random plasma glucose value of
- ≥ 200mg/dl [11.1 mmol/L] in a patient with hyperglycaemic crisis or with classic symptoms of hyperglycaemia[7]
- Diagnosis requires two abnormal screening test results, either from the same sample or in two separate test samples. Second test from different sample should be performed without delay.

▶ If the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed.

▶ If two different tests (such as A1C and FPG) are both above the diagnostic threshold from a single or two samples also confirms the diagnosis.[8]

- If patients have test results are marginal then after discussion of signs and symptoms with the patient, test repetition is advised in 3–6 months.[9]
- In a symptomatic or hyperglycaemic crisis patient, diagnosis can be made random blood glucose level of ≥200 mg/dl.

Otherwise following criteria should be used
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.

OR

2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT (performed on WHO criteria).

OR

A1C ≥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.[10]

- Patient should consume at least 150 g of carbohydrate on the 3 days prior to oral glucose tolerance test.[11]

Diagnosis of prediabetes

- It is a term used for the patient who has abnormal carbohydrate metabolism but blood glucose levels are below the diabetes diagnostic values.[12]

- Impaired fasting glucose (fasting glucose level of 100-125 mg/dl), impaired glucose tolerance (2-hour plasma glucose of 140-199 mg/dl in OGTT) or HbA1c of 5.7-6.4 % defines prediabetes.[13]
- It is not a separate clinical disease but a risk factor for development of diabetes.[14]

Diabetes Remission Criteria

Lifestyle modification in new onset diabetes can lead to diabetes remission.

- Remission is defined as a return of HbA1c to less than 6.5% that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose lowering pharmacotherapy.

Monitoring of blood glucose in people with Type 2 diabetes

Introduction: Glycaemic control is assessed by:

1. A1C measurement.
2. Continuous glucose monitoring (CGM) using time in range (TIR) and/ or glucose management indicator (GMI).
3. Blood glucose monitoring (BGM).

- A1C is the tool used in clinical trials demonstrating the benefits of improved glycaemic control and is therefore considered the gold standard in the monitoring of long-term complications of diabetes.
- CGM serves an increasingly important role in the management of the effectiveness in many patients with type 1 diabetes and in selected patients with type 2 diabetes. Individuals on a variety of insulin regimens can benefit from CGM with improved glucose control, decreased hypoglycaemia, and enhanced self-efficacy. In recent years, CGM is now a standard method for glucose monitoring for most adults with Type 1 diabetes.[15]
- BMG also called the serial monitoring of blood glucose (SMBG) is done by the patient at home and is the most effective way of self-management of diabetes. BMG is thus an integral part for effective therapy of patients taking insulin.[16]

Recommendations for glycaemic assessment

1. Assess glycaemic status (A1C or other glycaemic measurements such as time in range or glucose management indicator) at least two times a year in patients who are meeting treatment goals (and who have stable glycaemic control).
2. Assess glycaemic status at least quarterly and as needed in patients whose therapy has recently changed and/or who are not meeting glycaemic goals.

Glycaemic targets:

Sub Category	Fasting Blood Glucose FBG mg/dl	Random Blood Glucose RBG mg/dl	Bed time Blood Glucose	HbA1c%
Recent/without complications	80-120	80-160	100-140	6.5-7
With CCF*, CKD, CLD Autonomic Neuropathy	100-140	120-180	120-180	7.0-7.5

CCF-Congestive Cardiac Failure CKD-Chronic Kidney Disease CLD- Chronic Liver Disease

HbA1C: It reflects average glycaemia over approximately 03 months. It is the primary tool for assessing glycaemic control and it has a strong predictive value for diabetes complications. HbA1C testing should be performed routinely in all patients with diabetes at initial assessment and as part of continuing care. Measurements every 03 months determine whether glycaemic targets have been achieved and maintained.

- Perform twice a year in patients with stable glycaemic control.
- Perform quarterly in patients who have changed therapy or have not yet reached glycaemic goals.
- In most non pregnant T2DM, reasonable HbA1C is 7%.
- For selected individual patients with shorter duration of diabetes, long life expectancy, treatment only with metformin or lifestyle modification, no cardiovascular risk factor, strict HbA1c of 6.5% is advised if achievable.
- Patients with history of severe hypoglycaemia, extensive comorbid conditions, advanced microvascular and macrovascular complications, long standing diabetes, HbA1C of 8% may be considered.
- Disadvantages: A1C is an important measure of diabetes population health and of the risk of long-term complications. However, this long-term average glucose metric used alone may be insufficient to optimally guide a personalized

therapy change especially in patients using insulin since it cannot reveal the timings and extent of hypoglycaemia, hyperglycaemia and glucose variability. It does not measure day to day variability and cannot capture the daily regime of insulin dosing decisions and glycaemic excursions.[17]

- Limitations, A1C does not relate with patients CGM or BMG levels in patients with haemoglobin variants and conditions like end stage renal disease, pregnancy, recent blood transfusion, haemolytic anaemia, or erythropoietin therapy. These may result in discrepancies between patients' true mean glycaemia and A1C results.

A1C and Microvascular Complications: DCCT (Diabetes Control and complication Trial): A randomized control prospective trial of intensive mean A1C about 7% versus standard mean A1C of 9% glycaemic control in patients with type 1 diabetes, showed that better glycaemic control has 50 to 76% reductions in rates of development and progression of microvascular complications. A1C targets of <7% has been shown to reduce the micro vascular complications of type 1 & type 2 diabetes when instituted early in the course of disease.

- Glycaemic control is best evaluated by the combination of results from BMG/CGM AND A1C.

Self -Monitoring of Blood Glucose (SMBG):

- Daily SMBG is superior to less frequent monitoring.
- Frequency however varies according to the regimen and the affordability of the patient.
- **Types: 1. Low Intensity SMBG:** Two times/week (pre breakfast +bedtime). For most controlled non-affording T2DM and geriatric patients (age > 70 years) controlled with or without comorbid conditions. 2. Moderate Intensity SMBG: Two times daily (pre breakfast + one post meals can be suggested). For newly diagnosed or un-controlled non affording T2DM and controlled affording T2DM plus geriatric patients. 3. High Intensity SMBG: SMBG can be done 4 to 5 times every day or on alternate days until target blood glucose is achieved. Once the target is achieved, SMBG can be done 3 times (pre breakfast and Pre- and Post-meal of major meal or other meals as required every 4th or 5th day or as required). 4. Intensive Intensity SMBG: For pregnant women on MNT or on metformin a total of 14 readings per week including pre-breakfast and 1h PPG or 2h PPG are suggested.

Continuous Glucose Monitoring (CGM):

- Standardized, single-page glucose reports from continuous glucose monitoring (CGM) devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices.
- CGM is rapidly improving diabetes management. Benefits include improved glucose control, decreased hypoglycaemia episodes, enhanced self-efficacy. It also shows trends in hypoglycaemia, hyperglycaemia and glucose variability some of which warrant immediate therapeutic action.
- A recent study using modern CGM technology concluded that 10 to 14 days of CGM data provide a good estimate of CGM metrics for a period of 3 months. Ten days CGM data is usually sufficient for an estimate of average glucose, time in range and time in hyperglycaemia. 14 days of CGM data provides a better estimate of time in hypoglycaemia and glucose intra and inter day variability.
- Time in range:

As stated in recommendations, TIR is a useful metric of glycaemic control and it correlates well with A1C in most studies. It is the amount of time a patient spends in the target blood sugar range (70-180 mg/dl). Most people with type 1 and type 2 diabetes should aim for a time in range of at least 70% of readings that makes 17/24 hours each day to be in range (70 to 180mg/dl). Acceptable time below the range with glucose of below 70mg/dl is <4% (58 mins) and glucose below 54mg/dl is <1% (14 mins). While acceptable time above the range with glucose above 180 mg/dl is <25 % (6h) and above 250 mg/dl < 5% (1 hr 12 mins) is acceptable.

Glucose Management Indicator (GMI):

CGM data for at least 10 to 14 days provides sufficient material to generate a representative CGM- derived mean glucose value for a given individual. From this mean glucose value and by using a standard formula, a value some have called an "estimated A1C" / eA1C can be generated, intended to approximate the value of a simultaneously measured laboratory A1C. This CGM derived mean glucose value would be entered into a

standardized formula to generate a value similar to the previous eA1C value and is expressed in the same units but the name of the metric will be changed. The new name agreed upon to replace estimated A1C is Glucose Management Indicator (GMI).

"Glucose control Indicator "or" Glucose management Indicator" emerged as a leading modality to replace eA1C. The term GMI is intended to convey that this is a measure derived from glucose values and it provides information about the current state of a person's glucose management.

GMI (%) =3.31+0.02392× (mean glucose in mg/dl)

Correlation between BGM and A1C:

The correlation between A1C levels and mean glucose levels was based on the international A1C- Derived Average Glucose (ADAG) study. This assessed the correlation between A1C and frequent BGM and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes, and an empirical study of the average blood glucose levels at premeal, postmeal, and bedtime associated with specified A1C levels using data from the ADAG trial. The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation (r 5 0.92) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the HbA1C test. Clinicians should note that the mean plasma glucose numbers are based on 2,700 readings per A1C in the ADAG trial. In a recent report, mean glucose measured with CGM versus central laboratory–measured A1C in 387 participants in three randomized trials. This demonstrated that A1C may underestimate or overestimate mean glucose in individuals. Thus, as suggested, a patient's BGM or CGM profile has considerable potential.[18]

Hypoglycaemia:

Levels of hypoglycaemia: Level 1 Glucose <70 mg/dL (3.9 mmol/L) and >54 mg/dL (3.0 mmol/L) Level 2 Glucose <54 mg/dL (3.0 mmol/L) Level 3 A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia.[19]

Situations that increase risk of hypoglycaemia: when fasting for laboratory tests or procedures, delayed meals, during and after the consumption of alcohol, during and after intense exercise, and during sleep.

Occurrence and risk for hypoglycaemia should be reviewed at every encounter and investigated.[20]

Treatment:

Glucose (approximately 15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if blood glucose monitoring (BGM) shows continued hypoglycaemia, the treatment should be repeated. Once the BGM or glucose pattern is trending up, the individual should consume a meal or snack to prevent recurrence of hypoglycaemia. B Glucagon should be prescribed for all individuals at increased risk of level 2 or 3 hypoglycaemia; and it should be made available when needed. Caregivers, school personnel, or family members providing support to these individuals should know where it is and when and how to administer it.[21]

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CHAPTER 3

Non-pharmacological treatment of diabetes Mellitus: Lifestyle modifications (LSM)

Life Style Modifications (LSM) are the first and foremost component of T2DM management. Unbalanced eating habits and inadequate physical activity are main contributors in the development of diabetes.[1] LSM not only improves glycaemic control but is also helpful in modest and sustained weight reduction which is specifically important in newly diagnosed as well as in chronic cases of diabetes.[2,3]

The key components of lifestyle modifications include:

- Diabetes self-management education.
- Medical Nutrition Therapy (MNT) comprising of healthy eating patterns.
- Regular and adequate physical activity
- Sufficient amounts of sleep, and
- Smoking cessation with avoidance of all tobacco products, in any form (like Huqa, Sheesha, Naswar, Paan, Gutka).

3.1: Diabetes Self-Management Education:

Diabetes education is the most important element of management.[4] This focuses on empowerment of patient to decide about their own management plan under the guidance of their doctor. The continuing management of diabetes requires the person living with it to be able to make simple decisions regarding meals, exercise and medications. It is also significant that people with diabetes should be able to do self-monitoring of blood glucose, examination and care of feet and recognition and correction of hypoglycaemia.[5] Diabetes education should be commenced at the time of diagnosis and then annually with reinforcement at frequent follow ups for adherence.

- Set individualized target glycated haemoglobin (HbA1c) levels with the patient, and provide a level of care to achieve and maintain that target.
- Offer self-monitoring of blood glucose as an integral part of self-management, and agree when it should be performed and how it should be interpreted and acted upon. Also never miss to bring this record to the doctor on the next visit. This is one of the most important information for health care providers, because based on this record, the medicine will be modified.
- When starting insulin therapy, employ a structured training programme with active dose titration.

Following points should specially be emphasized;

3.1.1: Hypoglycaemia

Hypoglycaemia is defined as blood glucose level less than 70 mg/dl[6] resulting from an imbalance between glucose supply, glucose utilization, and current insulin levels. The associated symptoms are due to sympathetic overstimulation as well as due to neuroglycopenia. Recognizing hypoglycaemia is important so that steps can be taken to prevent a medical emergency. Symptoms include trembling, sweating, palpitation, change in vision, hunger, headache, mood swings, behaviour changes, lack of coordination, inattention and confusion. When severe, seizures and loss of consciousness may occur. People with T2DM should be able to recognize signs and symptoms of hypoglycaemia and know the immediate actions required to correct this condition (see chapter on acute diabetic emergencies).

3.1.2: Hyperglycaemia:

High blood glucose levels can lead to acute complications like hyperosmolar hyperglycaemic state, lactic acidosis or even DKA, or chronic micro or macro vascular complications. Regular blood glucose testing is helpful as patients often do not have symptoms. Short-term symptoms of high blood glucose include polyuria, polydipsia, nocturia, blurred vision, non-healing wounds and fatigue. A number of conditions or factors can contribute to hyperglycaemia. Lack of proper physical activity, taking carbohydrate rich food more than usual without adjusting insulin or oral medicines, any illness or psychosocial problem leading to excessive stress and forgetting or intentionally skipping medicines or insulin are common contributing factors. Detailed history along with assessment of behaviour is essential to correctly diagnose the reason. Self-monitoring of blood glucose should be emphasized and possible intensification of medicines or insulin maybe done.[5] (See chapter on acute diabetic emergencies).

3.1.3: Self-monitoring of blood glucose:

The required frequency of monitoring should be advised (varies from person to person). Adherence to this frequency should be emphasized whenever possible.

3.1.4: Signs and Symptoms of Foot Problems:

People with diabetes should be educated about warning signs of foot problems and daily foot care (see chapter 9).

3.1.5: Sick Day Rules:

When unwell, patients become more insulin-resistant and can sometimes develop complications. People with diabetes should be educated about sick days and common illnesses like flu, fever, sore throat, diarrhoea, vomiting, urinary tract infection or any other such ailment.

- Self-monitoring of blood glucose should be frequent (4-6 times/day).
- Early physician advice should be sought regarding all medicines.
- Plenty of liquids including water or soup should be taken. Avoid sugary or caffeine containing drinks.
- Refer for hospitalization if symptoms persist or in case of uncontrolled blood glucose levels.

3.2: Medical Nutrition Therapy:

- For people with diabetes, the most challenging part of the treatment plan is determining what to eat, how much to eat and following a meal plan.
- Meal planning should be individualized based on factors like patient preferences, BMI, degree of hyperglycaemia, co-morbidities etc. MNT should ideally be provided by a registered dietitian (RD) where possible who is knowledgeable and skilled in providing diabetes-specific MNT.
- Emphasise portion control and healthy food choices for all those with type 2 diabetes.
- Address the need for consistency in day-to-day carbohydrate intake; as well as the importance of eating a healthy, high-fibre breakfast, and not skipping meals, to lessen the risk of unhealthy eating late at night.

Physician Delivered Nutrition Therapy Algorithm: A physician delivered nutrition counselling algorithm shown to be effective in primary care settings includes five steps:

a) Address the agenda to the patient to clarify need for nutrition counselling.

b) Assess patient's motivation, past diet experience and current diet.

c) Advice "Based on your health risks and current diet, I recommend that we focus on (high fat intake, excess calories, inadequate intake of fruits and vegetables)."

d) Assist to formulate a plan including two or three simple and specific dietary goals, addressing possible barriers and ways to handle them. Determine whether the patient needs additional information or help; refer to dietician as needed.

e) Arrange frequent follow-up, either by phone contact, email or return visit.

Focus on diet quality and dietary patterns:

A. Balanced food group intake:

- Frequent and excessively large portions of foods having high proportion of fats (especially saturated ones), sugar, starch and salt (e.g. bakery items, fast foods and fried products) must be discouraged.[7]
- Intake of fish, skimmed milk and yogurt, green leafy vegetables, should be encouraged to increase nutrient density of diets.
- Each meal should have food from several food groups particularly, high protein food, fresh or lightly cooked vegetables and fruits
- In a day, for most adults consuming two servings of high protein foods (e.g. 6 oz meat), 2 servings of foods from milk group (e.g. two cups of milk/yogurt), and five servings of fruits and vegetables (e.g. 1 cup cooked vegetables, 1 cup salad, one seasonal fruit) are essential to provide sufficient protein, minerals and vitamins.

B. Food safety:

In view of lack of local regulatory controls on food quality, intake of freshly cooked/prepared foods of known origin should be strongly recommended for people with diabetes in Pakistan.

C. Number of meals:

Number of meals should be determined according to person's lifestyle, metabolic status and medical treatment options. For example, frequent small meals could help in

sustaining normoglycaemia and preventing hyperphagia in persons having insulin resistance and hyperinsulinaemia.

D. Energy and nutrients:

Energy: If feasible, energy requirement should be calculated individually for each subject using BMR estimation equations and incorporating activity level and stress factor. This can be done using energy estimation calculators.

- In case it is not feasible, energy requirement could be based on the basis of ideal body weight (IBW).
- For adults, energy intake could be in the range of 25 to 30 calories per kg of adjusted body weight (i.e.IBW+.25* excess weight). It has been found that in terms of glycaemic control, 30 kcal/kg of IBW was more acceptable energy level for obese person with diabetes.[8]

Protein:

- Adequate protein intake is important for controlling metabolic derangements, attaining normoglycaemia, preventing muscle loss and maintaining health and wellbeing.
- In Pakistani people with diabetes, protein intake has been found to be inadequate, so for most people increasing its quantity and quality needs to be recommended.
- For adult's, protein requirements range from 0.8 to 1.2 gram per kg body weight
- Person getting most of their proteins from vegetable sources need relatively higher amounts of proteins.
- Total protein intake in general and animal protein intake in particular should be distributed in different meals.
- In person having wheat as staple food and having difficulty in taking animal proteins or variety of vegetable proteins, lysine supplement could help in improving protein quality of diet.

Proportion of Fats and Carbohydrates:

Recent recommendations do not suggest any particular proportion of calories from fats or carbohydrates. Use of fats and foods high in carbohydrates (e.g. sugars and refined food from the cereal group) should be controlled according to energy requirements.

Carbohydrates:

- Monitoring the total daily carbohydrate intake (by carbohydrate exchanges) is the primary strategy in achieving glycaemic control.
- The total amount of carbohydrate intake is the predominant factor in controlling the post-prandial blood glucose levels
- Meal plan with portion control and individualised diet plan is ideal. Observing the amount of carbohydrates matching with available insulin is the main strategy for good post-prandial control.
- People with diabetes should deduct their CHO intake in the form of rice and roti gradually to reduce their weight and improve their glycaemic control.
- Carbohydrate intake (fruits, milk, yogurt and starchy food) ideally should not be consumed together.
- Consistency in carbohydrate intake results in improved glycaemic control thus education for carbohydrate counting/ estimation must be provided.
- For person taking insulin or insulin secretagogues it is essential that they monitor and control carbohydrate content of their food to prevent severe hypoglycaemia. For good health, carbohydrate intake from vegetables, fruits, whole grains, legumes, and dairy products are advisable.
- People with diabetes and those at risk for diabetes should limit or avoid intake of sugar-sweetened beverages (from any caloric sweetener including high-fructose corn syrup and sucrose) to reduce risk for weight gain and worsening of cardio-metabolic risk profile.
- As carbohydrate intake (in form of roti, snacks, sugar, sweets etc.) is in general high in Pakistan, decreasing its intake should be encouraged.

Fats:

- Use of trans fats (ghee, margarine) should be firmly discouraged. Use of food containing high amounts of fats especially palm oil needs to be limited.
- Use of oils rich in mono and polyunsaturated fats e.g. mustard oil, canola oil, and corn oil in moderate amounts should be encouraged.

- Intake of omega 3 fats (from fish, flax seed etc.) to balance intake of n3/n6 fatty acids (present in vegetable oils) should be suggested.
- Use of oils high in monounsaturated fats (e.g. olive oil) in place of refined carbohydrates could be recommended as it is cardio protective and helps in glycaemic control.
- As fat intake (in form of fat in curries, fried snacks, fat as topping on foods etc.) is very high in many regions of Pakistan, decreasing its total intake should be encouraged.

3.3: Physical Activity (PA):

Physical activity includes regular movement such as walking, structured exercise such as running, swimming or cycling and weight training exercises.[9] PA is an effective intervention in improving glycaemic control, blood pressure and lipid levels in addition to improving sense of wellbeing.[10] Simplest form of physical activity like 30 min walk 5 days a week can result in significant benefits in metabolic control, energy expenditure, better work capabilities, and improvement in cardiovascular risk.[11] Simple walk with moderate intensity is safe in majority of the people.

- Advising physical activity of greater intensity requires careful history taking and evaluation for presence of any co morbidity. People with proliferative retinopathy or severe non proliferative retinopathy and recent or active cardiac problem should be advised simple walk according to the situation. People with compromised visual acuity should be supervised during walk.
- Presence of autonomic neuropathy may increase the risk of postural hypotension, decreased cardiac responsiveness to increasing need of cardiac output or hypoglycaemic unawareness. In such cases commence with low intensity and duration, gradually increasing to tolerable levels.
- Peripheral neuropathy leading to feet at risk should be evaluated. If present, moderate intensity walk with appropriate footwear is advisable.
- If patient has not been active at all, start slowly and increase activity over a period of time. Simple walk for at least 30 min, 5 days a week is enough in initial phases or simple aerobics that increase heart rate 60-70% of maximum(Maximum Heart Rate = 220 - age in years).
- In willing people without any contraindication, structured exercises like running, swimming or cycling can also be introduced.
- Household chores like mopping, gardening, laundry etc. should also be encouraged to enhance active hours in a day.
- Minimal but significant changes in lifestyle like using stairs instead of taking elevators, parking car at a distance from workplace, keep walking while conversing on phone etc. can bring significant change in activity status of a person.
- People should be educated about hypoglycaemia and its management. People requiring insulin or those on potent hypoglycaemic agents need to be aware of potential delayed hypoglycaemia 6-12 hours after cessation of the physical activity. A quick glucose source should be kept available during exercise.
- Proper warm up and cool down is advised. The people with diabetes should be advised to stop if cardiovascular symptoms like chest pain, severe exhaustion or unusual breathlessness develop.
- People with intermittent claudication should generally be encouraged to continue as these symptoms will improve with time.
- Plenty of water should be taken to avoid dehydration. In extremes of weather, indoor alternative exercises are favoured.
- People should be advised to examine their feet for any redness, blister or any sign of irritation after exercise. Properly fitting socks and joggers should be worn during exercise.

Adequate Sleep:

All patients should be advised to sleep on average approximately 7 hours per night. Evidence supports an association of 6 to 9 hours of sleep per night with a reduction in cardiometabolic risk factors, whereas sleep deprivation aggravates insulin resistance, hypertension, hyperglycaemia, and dyslipidaemia and increases inflammatory cytokines.

Smoking Cessation:

- Smoking cessation is another important component of lifestyle therapy and involves avoidance of all tobacco products including pan, gutka, huqqa, niswar, sheesha and e-cigarettes.

- Adverse effects of smoking on health and its association with various complications should be emphasized at each clinic visit. Effective intervention therapies for quitting smoking should be offered to all patients.

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CHAPTER 4

Pharmacological management of diabetes

Overview

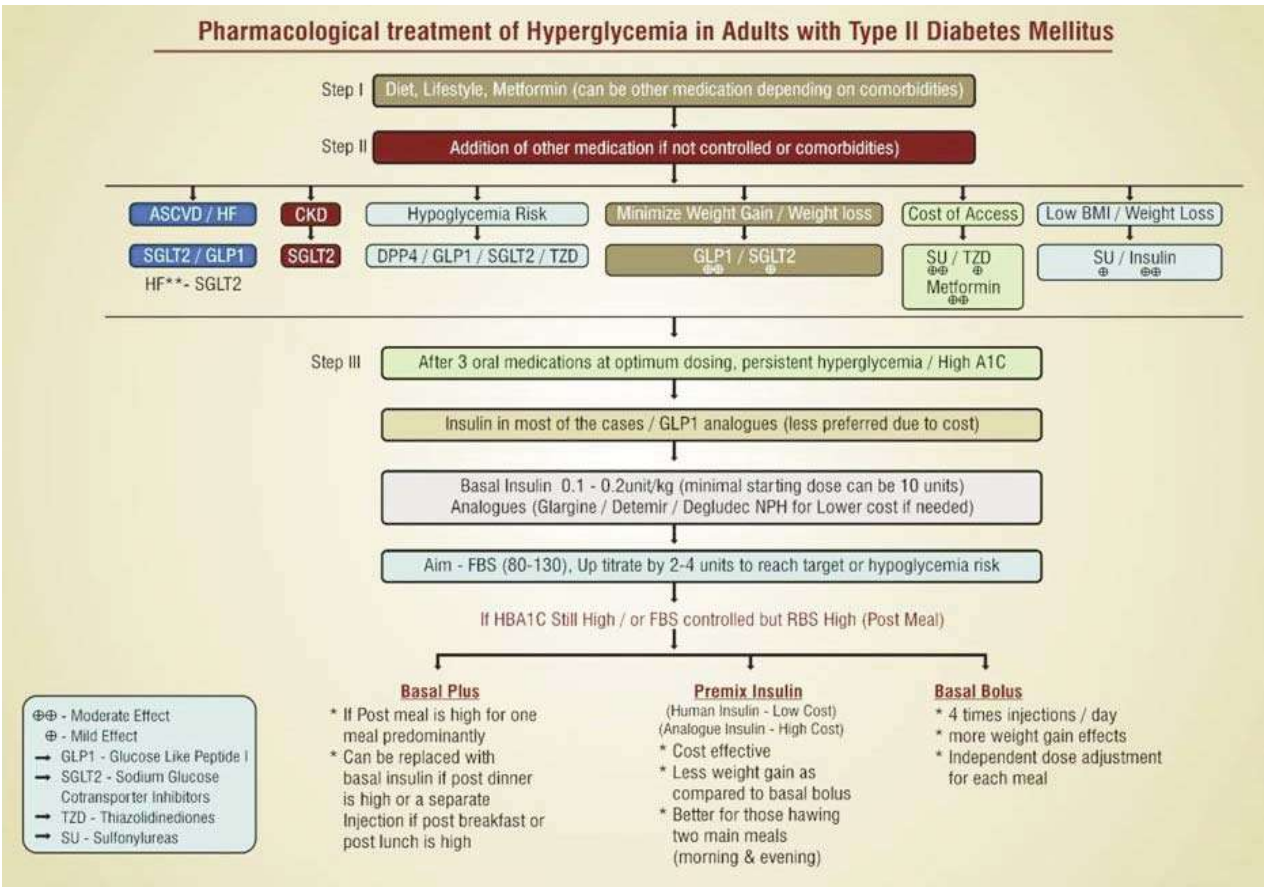
- The choice of pharmacological agent must be individualized, based on attributes specific to both patients and the medications.
- The choice of therapy also depends on the patient's age, BMI, duration of disease, glycaemic status, risk of hypoglycaemia, cardiac, cerebrovascular, renal function and financial status.
- The choice of therapy should take into consideration ease of use and availability. The therapeutic regimen should be as simple as possible to optimize adherence.
- Comorbidities must be managed for comprehensive care, including management of lipid and blood pressure abnormalities and treatment of other related conditions.
- Any of the selected regimes should be evaluated every three months with HbA1c and SMBG. If HbA1c is not available, SMBG and/or lab records can be helpful. Patients should be assessed for possible side effects of drugs, including hypoglycaemic events, weight gain, fluid retention, hepatic or renal impairment or cardiovascular risks. They should also be assessed for co morbidities, drug adherence and psychosocial issues. [1]
- Metformin may be prescribed to all patients along with lifestyle modifications, irrespective of their baseline BMI, if there are no contraindications. [2] If metformin is contraindicated or is not tolerated, GLP1 agonists or SGLT2 inhibitors can be prescribed as preferred agents. DPP4 Inhibitors, sulphonylureas or alpha glucosidase inhibitors can be used as an alternative. [3]
- In newly diagnosed patients with T2DM presenting with signs and symptoms of hyperglycaemia and having an HbA1c >8.5%, a second oral agent or insulin should be considered along with metformin. Initial combination of sub maximal doses of antihyperglycaemic agents produces better and quicker response than maximum doses of monotherapy. [3-5]
- Individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or at high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as a part of the glucose- lowering regimen and cardiovascular risk reduction, independent of A1C and in consideration of patient-specific factors.[6]
- Metformin may be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycaemic and metabolic benefits.[6]
- In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible.[6]
- If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy and durability of treatment effect.[6]
- Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed. [6]

(Algorithm 1)

Factors influencing

Management strategies clinical factors:

- Age
- Weight
- Atherosclerotic cardiovascular disease (ASCVD) and indicators of high ASCVD risk, chronic kidney disease (CKD), and heart failure (HF)
- Degree of hyperglycaemia
- Risk of hypoglycaemia / hypoglycaemia unawareness
- Socio-economic status
- Individual preference



Algorithm 1

Pharmacological factors

- Efficacy in glycaemic control
- Cardiovascular benefits.
- Renal benefits
- Risk of hypoglycaemia
- Risk of weight gain
- Drug interactions
- Side effects
- Cost and availability

Rationale and evidence

Available Therapeutic Agents in Pakistan
Metformin:

- Metformin is currently the drug of first choice for the treatment of hyperglycaemia in DM, without stimulating insulin secretion, promoting weight gain or causing hypoglycaemia. [2, 3]
- Metformin is an insulin-sensitizer, which causes reduction in insulin resistance and a significant decrease in plasma fasting insulin levels. Metformin monotherapy can reduce HbA1c by 1.1%. [7]
- It also provides benefits of weight stability or slight weight reduction. [8]
- Metformin is an effective, safe, inexpensive drug and may reduce risk of cardiovascular events and death.[9]
- It is generally well tolerated. Most commonly reported side effects are anorexia, nausea, diarrhoea and a metallic taste.
- These effects can be minimized with gradual dose titration and given with meals.
- Lactic acidosis is the only serious side effect. However, its risk incidence is extremely low.[10]
- It is contraindicated in CKD Stage 4 and 5 (eGFR<30).[11] If eGFR is not available metformin

should be discontinued at serum creatinine>1.5mg/dl in men and > 1.4 mg/dl in women.

- Metformin is excreted through the kidneys. The reduction in renal clearance of metformin is considered as an important risk factor for lactic acidosis it should be started at a low dose and titrated upwards until the required glycaemic targets are achieved or another oral agent is added in regime.
- It may also be associated with Vit. B^{12} deficiency in some cases with long term use.
- The maximum dose is up to 2000 g in divided doses. It should be started at a low dose, typically 500mg twice daily, with upward titration if desirable control of hyperglycaemia is not achieved. The drug is well tolerated.
- Metformin is available in an immediate-release form for twice or thrice daily dosing or as an extended-release form that can be given once daily.

SGLT2 inhibitors

- Sodium-glucose co- transporters (SGLT2) are present in proximal tubules of kidneys. Kidneys filter glucose freely, 90% of which is reabsorbed in the proximal tubules by the action of SGLT2.
- SGLT2 inhibitors lower HBA1c by 0.7-1%. Available SGLT2 agents in Pakistan are dapagliflozin (5 and 10 mg), empagliflozin (10 and 25 mg) and Ertugliflozin (5 and 15 mg). .
- In patients with type 2 diabetes and heart failure and/or kidney disease, all SGLT2 inhibitors have shown salutary effects. [12]
- Empagliflozin and canagliflozin have been shown to decrease atherosclerotic cardiovascular morbidity and mortality in patients with type 2 diabetes and overt CVD.[13]
- Dose of dapagliflozin is 10 mg daily, but it is recommended to start with 5mg initially. Dose of empagliflozin is 10 mg daily, but higher dose of 25 mg daily can be used.
- Avoid use of SGLT2 inhibitors in patients with frequent bacterial urinary tract infections or genitourinary yeast infections, low bone density and high risk for falls and fractures, foot ulceration, and factors predisposing to diabetic ketoacidosis (DKA; eg, pancreatic insufficiency, drug or alcohol abuse disorder, ketogenic diets) because of increased risk while using these agents.[14]
- Volume status and renal function (serum creatinine with estimation of glomerular filtration rate [eGFR]) should be assessed prior to starting an SGLT2 inhibitor and periodically thereafter.[15]
- Patients taking SGLT2 inhibitors should be monitored for signs and symptoms of genitourinary tract infections and foot ulceration.[8]
- Efficacy of SGLT2i is decreased in chronic kidney disease and is contraindicated in patients with eGFR less than <30.[2,3,16]

GLP 1 receptor agonists

- Glucagon-like peptide 1 (GLP-1) is known for the 'incretin effect', which results in a glucose dependent increase in insulin secretion and suppression of glucagon secretion from the pancreas.
- GLP-1RAs improve glycaemic control, reduce patient weight and improve patient-reported outcomes when administered as monotherapy or add-on therapy to other glucose- lowering drugs.
- Meta-analyses of the trials reported to date suggest that GLP-1 receptor agonists and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in patients with type 2 diabetes and established ASCVD.[15]
- In patients with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events.[15]
- GLP-1RAs are generally well tolerated with a very low intrinsic risk of hypoglycaemia.
- Also suppress pancreatic glucagon output, retard gastric emptying and diminish appetite. This usually results in weight reduction.
- Are expensive and administered subcutaneously on a daily or weekly basis.
- Can reduce HbA1c by about 0.6% to 0.8% when used as monotherapy.[17,18]

- Once-weekly administration of GLP-1RAs may improve treatment adherence and satisfaction relative to more frequent treatment.
- Patients should be advised to seek medical care if they experience unexplained persistent severe abdominal pain.
- Available agents in Pakistan are Liraglutide (Prefilled, multidose pen that delivers doses of 0.6mg, 1.2mg, or 1.8 mg, to be taken once a day), Semaglutide (Prefilled, multidose pen that delivers doses of 0.25mg, 0.5mg, or 1.0 mg, to be taken once weekly), Dulaglutide (1.5mg single dose pen, taken once weekly), and Lixisenatide 50 microgram and 33 mcg with Insulin glargine in a fixed ratio combination.

Dipeptidyl peptidase IV inhibitors (DPP4 Inhibitors)

- The oral dipeptidyl peptidase IV (DPP-4) inhibitors or incretin enhancers, increase circulating concentrations of active GLP-1 and GIP.[19]
- Lower HbA1c by approximately 0.5-1.0% and are weight neutral.[19,20]
- Proven efficacy when combined with metformin, sulfonylurea or both metformin and sulfonylurea.
- Low risk of hypoglycaemia.
- Recent cardiovascular studies have shown that these agents do not increase the CV risk.[19,20]

Sulphonylureas (SU)

- SUs reduces plasma glucose levels by enhancing insulin secretion, with an average A1c reduction of 1.5%.[21]
- The major adverse side effect is hypoglycaemia. The risk is higher in renal impairment, liver cirrhosis and in the elderly.
- Weight gain is also a common side effect.[19]
- Second generation SUs (gliclazide, glimepiride) have a lower risk of hypoglycaemia and weight gain.
- Highly protein bound therefore administration of drugs like non-steroidal anti- inflammatory drugs (NSAIDs), antithyroid drugs, sulpha drugs, anticoagulants and α- blockers can displace them, increasing the risk of hypoglycaemia.

Alpha glucosidase inhibitor (AGI)

- AGIs are Saccharides which act as competitive inhibitors of enzymes required to digest carbohydrates, including starch and table sugar, thus controlling postprandial hyperglycaemia.
- Can reduce HbA1c by 0.4 to 0.9%
- Major side effects are bloating and flatulence. Hence usually not well tolerated. Side effects can be avoided by slow titration of dosage.

Thiazolidinedione (TZDs)

- These insulin sensitizers are PPAR gamma agonists.
- Major side effects include oedema, weight gain, risk of congestive heart failure (CHF) and increased risk of fractures.
- This significantly limits their clinical use.[22]
- Have conflicting findings regarding myocardial infarction (MI) risk. However, they should not be used in NYHA class 2 patients.[2,3,22]
- Inconclusive evidence for their association with bladder cancer.[22]
- The starting dose of Pioglitazone is 15 mg /day and can be titrated to maximum dose of 45 mg/day.

Repaglinide

- Relatively short-acting stimulator of insulin secretion (<6 hours).
- Acts by binding to ATP dependent potassium channels on pancreatic beta cells.[23]
- The main risk is hypoglycaemia and weight gain.
- Mainly excreted through hepatic route, hence is safe in renal compromised patients.[23]

Insulin

Insulin therapy is often required in people suffering from type 2 diabetes to optimize blood glucose control.[3] Insulin therapy in type 2 diabetes is recommended for patients who are:

- Unable to reach glycaemic targets with lifestyle modification (diet and exercise) or with a maximum dose of oral hypoglycaemics or noninsulin injectables, e.g., Glucagon like peptide-1 (GLP-1) receptor agonist

Table-1: Insulin Commercially Available in Pakistan

Type of Insulin	Br and Name	Manufacturer	Dosage from
Ultra-short acting/Rapid-acting Insulin analogues (Bolus)			
Lispro	Humalog	Eli Lilly	Vial/Cartridgen/Pen
Aspart	NovoRapid	Novo Nordisk	Vial/Cartridgen/Pen
Glulisine	Apidra	Sanofi Aventis	Vial/Pen
Short-acting/Regular Human Insulin (Bolus)			
Regular or Insulin R	Humulin-R	Eli Lilly	Vial
	Actrapid	Novo Nordisk	Vial/Cartridgen
	Insuget-R	Getz Pharma	Vial
Intermediate-acting Insulin (Basal)			
NPH (Neutral Protamine Hagedorn)	Humulin-N	Eli Lilly	Vial
	Insulatard	Novo Nordisk	Vial/Cartridgen
	Insuget-N	Getz Pharma	Vial
Long-acting Insulin Analogues (Basal)			
Insulin Glargine (U-100)	Lantus	Sanofi Aventis	Vial/Pre-filled pen
Insulin Determir	Levemir	Novo Nordisk	Pre-filled pen
Ultra-Long acting Insulin Analogues (Basal)			
Insulin Glargine (U-300)	Toujeo (1.5)	Sanofi Aventis	Pre-filled pen
	Toujeo Max (3 ml)		
Pre-mixed human Insulin (Intermediate-acting NPH + Short-acting Regular-R) (70% N 30% R)			
NPH + Regular	Humilin-70/30	Eli Lilly	Vial/Cartridge
	Mixtard-70/30	Novo Nordisk	Vial/Cartridge
	Insuget 70/30	Getz Pharma	Vial
Pre-mixed Analogues [NPL(Neutral Protamine Lispro) + Lispro (Ultra-short acting Analog)]			
NPL + Lispro	Humalog Mix 25	Eli Lilly	KwikPen/Cartidge
	Humalog Mix 50	Eli Lilly	
Pre-mixed Analogues [70 % Insulin Aspart Protamine +30% Insulin Aspart (Ultra-short acting Analogy)]			
Aspart Protamine + Aspart	Novo Mix 30	Novo Norkish	FlexPen
	Novo Mix 50		
Pre-mixed Ultra-long acting and Ultra-short acting Analogues (70% Insulin Degludec and 30 % Insulin Aspart)			
Degludec + Aspart	Ryzodeg	Novo Nordisk	FlexPen
Insulin + GLP-1 combination			
Xultropy (Long acting GLP-1)	3.6mg Liraglutide/ml		
	100U degludec/ml	NovoNordisk	Flexpen
Soliqua (short acting GLP-1)	50mcg and 33mcg preparations +		
	100 U glargine/ml	Sanofi Aventis	Penfill

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- Unable to tolerate oral hypoglycaemics or non-insulin injectables.
- Being treated for acute complications of diabetes (DKA, HHS).
- Undergoing surgery.
- Unable to use oral hypoglycaemics and non-insulin injectables due to allergies, renal or hepatic disorders.

Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes, who are symptomatic and/ or have A1c ≥ 10% (86 mmol/L) and/or blood glucose levels ≥ 300 mg/dL and if there is evidence of ongoing catabolism (weight loss).[24,25]

Insulin can be categorized according to either duration of action ranging from rapid acting insulin to short acting, intermediate acting, long acting and very long-acting insulin or their source as human or analogue insulin.

- The human insulin is less expensive than analogues, hence more affordable.
- The dose should be adjusted at regular intervals. Less expensive human insulins are beneficial in most of the cases particularly if comprehensive education about preventing; identifying and

Table-2: Insulin Pharmacodynamics

Type of Insulin	Onset	Peak	Effective Duration	Meal Relation	Color
Ultra-short acting/Rapid-acting Insulin analogues (Bolus)					
Lispro Aspart Gluisine	< 15 mins	1 Hr	2-4 Hrs	15 mins or just before/ after meal	Clear
Short-acting/Regular Human Insulin (Bolus)					
Regular or Insulin R	0.5-1Hr	2-3 Hr	3-6 Hrs	30-45 mins before meal	Clear
Intermediate-acting Insulin (Basal)					
NPH	2-4 Hrs	4-10 Hr	10-16 Hrs	Not related with meal. Once, twice or thrice daily (6)	Cloudy
Long-acting Insulin Analogues (Basal)					
Insulin Detemir	0.8-2Hr (Dose Dependent)	Relativel y Flat	24 Hrs	Not related to meal Once daily - Morning or Evening. Also can be given twice a day. (1)	Clear
Insulin Glargine (U- 100)	2-4 Hr	Relativel y Flat	20-24 Hrs		
Ultra-Long acting Insulin Analogues (Basal)					
Insulin Glargine (U- 300)	2-4 Hr	Relativel y Flat	>24 Hrs	Not related to meal. Once Daily-Morning or Evening.	Clear
Pre-mixes Human Insulin (Intermediate-acting NPH + Short acting Regular R) (70% N 30% R)					
NPH+ Regular	0.5-1	Dual	10-16 Hrs	30-45 mins before meal	Cloudy
Pro-mixed Analogues [NPL (Neutral ProtamineLispro) + Lispro (Ultra-short acting Analogue)]					
NPL + Lispro	<15 Min	Dual	10-16 Hrs	15 min or just before/after meal	Cloudy
Pre-mixed Analogues [70% Insulin Aspart Protamine +30% Insulin Aspart (Ultra-short acting Analogue)]					
Aspart Protamine + Aspart	<15 Min	Dual	15-18 Hrs	15 min or just before after meal. Can ve given once twice or thrice daily (7,8)	Cloudy
Pre-mixed Ultra-long acting and Ultra-short acting Analogues (70% Insulin Degludec and 30% Insulin Aspart)					
Degludec + Aspart	<15 Mins	Dual	>24 Hrs	15 min or just before/after meal	Clear

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timely correction of hypoglycaemia has been imparted.

- Different types of insulin and their duration of action are discussed in the tables mentioned as commercially available insulins and insulin pharmacodynamics given at the end of chapter. (Table 1 and 2)

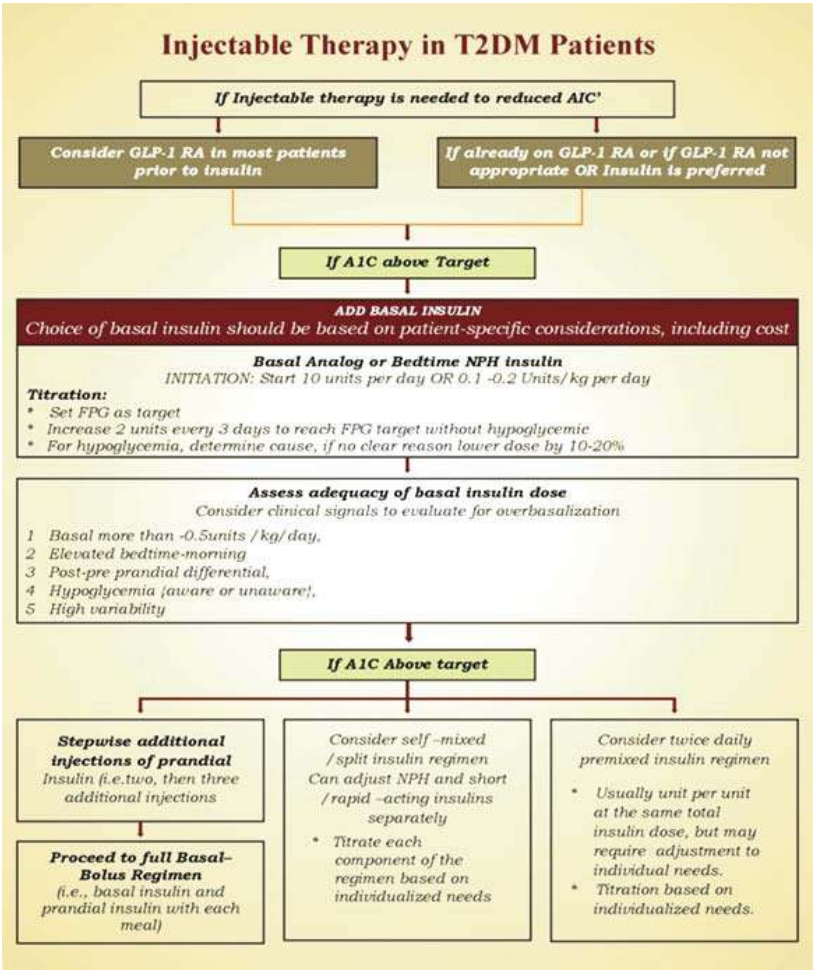
How to initiate insulin in people with T2DM?

If Fasting Blood Glucose Levels are high: (Algorithm 2)

- Basal insulin alone is the most convenient initial insulin regimen and can be added to metformin and other oral agents [2,3,24]
- A single dose of intermediate-acting insulin NPH or long-acting insulin Glargine U-100, Glargine U-300 or Detemir can be added at bedtime with the current oral therapy [6,23,24]
- To prevent hypoglycaemia, it is advised to initiate insulin with a starting dose estimated based on body weight (0.1–0.2 units/kg/ day) and the degree of hyperglycaemia, while adjusting the dose by increasing 2 units every 3 days based on the fasting blood glucose levels until the desired target is achieved.[23,24]
- In case of hypoglycaemia determine cause, if no clear reason reduce dose by 10-20% [26]
- SMBG should be done at least twice daily, usually before breakfast and before bedtime, but more frequent SMBG is recommended to meet goals of the therapy[24, 25]

Clinicians should be aware of the potential for over basalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose greater than 0.5 units/kg, high bedtime-morning or post-preprandial glucose differential (e.g., bedtime- morning glucose differential >50 mg/dL), hypoglycaemia (aware or unaware), and high variability. Indication of over basalization should prompt re-evaluation to further individualize therapy[26]

If post- prandial blood glucose levels are high:



Algorithm 2

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycaemic targets.

The following options can be considered:

- Continue the bedtime NPH injection and add a second injection of NPH before breakfast at a dose of 0.2 units per kg.19,20 Metformin, SGLT2 inhibitors, DPP-4 may need to be continued. Addition of GLP-1 or SGLT2 inhibitors may help to improve control in patients with suboptimal glycaemic levels requiring higher insulin doses, and may reduce the amount of insulin required in these patients[25]
- Add rapid-acting or short-acting insulin before the largest meal of the day. Initiate with a starting dose of approximately 4 units,18 while adjusting the dose by 1-2 units every 3 days until the desired target is achieved. [27]
- In case of hypoglycaemia determine cause, if no clear reason reduce dose by 10-20%. [26]
- Add once daily dose of premixed insulin with largest meal of the day.
- Switch to pre-mixed or free-mix (R and NPH) insulin twice a day before breakfast and dinner.
- Add GLP-1 receptor agonist to the basal insulin. The combination of GLP-1 receptor agonist and basal insulin is more effective in lowering glucose levels and has a lesser chance of weight gain and hypoglycaemia as compared to the intensified insulin regimen. However, cost is a major challenge in low socioeconomic countries like Pakistan.

Intensive insulin therapy

If the HbA1c target is still not being met on basal insulin along with single injection of rapid- acting insulin before the largest meal of the day, proceed to a basal-bolus regimen with either 2 or 3 injections of rapid-acting insulin before each meal i.e., before breakfast, lunch and dinner.[27]

Example of Intensive insulin regimen by using rapid acting insulin or intermediate or long-acting insulin in 70 kg man with type 2 diabetes. Assume he is consuming 75g carbohydrate at breakfast, 60g at lunch, and 90g at dinner. (Table 3)

Table-3: Intensive Insulin Regimens

Insulin	Pre-Breakfast	Pre-Lunch	Pre-Dinner	Bed Time
Rapid acting insulin analogue lispro, aspart, glulisine	6 U	4U	6U	
NPH	12U	0U	8U	
OR				
Rapid acting insulin analogue	5U	4U	6U	
Insulin Glargine OR Degludec OR				16U
Insulin detemir				16U

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- The dose of rapid acting analogues can be raised by 1 or 2 unit if extra carbohydrate (15-30g) is

ingested or if pre-meal blood glucose is >170mg/dl.

- The rapid acting insulin can be mixed in the same syringe with NPH insulin.
- Insulin glargine or insulin detemir must be given as a separate injection.

When initiating combination injectable therapy, metformin therapy should be maintained, while sulfonylureas and DPP- 4 inhibitors are typically weaned or discontinued. In individuals with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered.[26]

Few key points to go over with the patient before increasing the insulin dose:

Patients who are already on insulin and still have uncontrolled diabetes, before increasing insulin dose further, exercise and dietary compliance must be emphasized. Patient should be asked about the timing of insulin injection, dosing of insulin and proper storage of insulin. Patient should also be asked about insulin injection technique. The areas where insulin should be injected are abdomen, anterior and lateral aspect of thighs, buttocks or sparingly the tricep fold of arms. Inspection of site of Insulin injection is of utmost importance in these patients for redness, swelling, lipohypertrophy (hypertrophy of subcutaneous tissue due to injecting insulin at the same site repeatedly) and lipodystrophy (immune mediated disfiguring atrophy of tissues). Insulin is not effectively absorbed if any of these above-mentioned complications are present. Before changing insulin dose above issues need to be addressed if present. To avoid these complications best approach is to use sterile technique for insulin administration and the injection site should be rotated frequently.

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CHAPTER-5

Obesity And Diabetes

Key points:

Obesity, by itself not only renders one prone to Diabetes but also makes management of it quite challenging.

▶ There is substantial evidence that even modest weight reduction whether through lifestyle/behavioural interventions, weight reducing medicines, or Metabolic surgery can delay the progression from prediabetes to type 2 diabetes and improve glycaemic control.[1,2]

▶For those who are obese and do not have diabetes, a loss of 5% of body weight along with regular exercise can reduce risk of developing diabetes by over 50%.[3]

▶Those who have Prediabetes, life style change alone reduces the risk to progression to Diabetes by 58%.[4]

▶The importance of treating obesity is further heightened by data from all over the world showing that both obesity and diabetes increase risk for more severe coronavirus disease 2019 (COVID-19) infections.[5-7]

▶Treatment of obesity usually requires more than just dietary changes. It requires support and counselling, as well as Physical activity. Additionally, medication can supplement lifestyle modifications to help patients tackle weight problems.

▶BMI should be calculated for all patients and those with obesity should be referred for intensive, multicomponent behavioural interventions.

▶Increased physical activity should be recommended for weight loss in combination with diet and behavioural modifications.

▶Physicians should consider medications for weight loss in type 2 Diabetes patients with a BMI of ≥ 25 kg per m^2.

▶Type 2 Diabetes patients with a BMI ≥ 37.5 kg/m^2 and those with a BMI ≥ 32.5kg/m^2 who do not achieve durable weight loss and improvement in comorbidities (including hyperglycaemia) with nonsurgical methods should be considered for Metabolic Surgery referral.

▶Metabolic surgery may be considered as an option to treat type 2 diabetes in adults with BMI 27.5–32.4 kg/m^2 who do not achieve the same with nonsurgical methods.

Assessment

Measure height and weight and calculate BMI at first visit and then Annually.
Based on clinical considerations, such as the presence of comorbid conditions or significant unexplained weight gain or loss, weight may need to be monitored and evaluated more frequently.
Diet and behavioural interventions should be initiated in patients who are overweight.

Strategies for reducing body weight:

Creating a negative energy balance, i.e., consuming lower number of calories than spent is the only method for reducing body weight. Substantial and consistent negative energy balance induces lipolysis and weight loss. This could be achieved by decreasing energy intake and/or increasing energy expenditure. Energy intake could be decreased by modifying the amount, frequency and type of food consumed.
Energy expenditure could be increased by increasing voluntary physical activity and/or increasing basal metabolic rate.

Table-1: Weight Classifications[8]

Classification	Body mass index(kg/m^2)	Waist circumference
Underweight	<18.5	-
Normal Weight	18.5 to 22.9	Male <90cm Female <80cm
Overweight	≥23	-
At Risk	23 to 24.9	Male ≥90cm Female ≥80cm
Class 1 Obesity	25 to 29.9	
Class 2 Obesity	≥ 30	

Strategies that help in achieving negative energy balance include:

1. Lifestyle changes:

a. Diet: Lower consumption of energy

b. Physical Activity: Higher expenditure of energy

c. Behavioural therapy

2. Pharmacotherapy

3. Metabolic Surgery

1) Lifestyle changes: Diet, physical activity, and behavioural therapy to achieve and maintain >5% weight loss is recommended for most people with type 2 diabetes and overweight or obesity. Additional weight loss usually results in further control of diabetes and cardiovascular risk.

a) Diet Among patients with both type 2 diabetes and overweight or obesity who have inadequate glycaemic control and/or other obesity related medical conditions, modest and sustained weight loss improves blood glucose, blood pressure, and lipids and may reduce the need for medications to control these risk factors.[9,10]

Negative energy balance, and weight loss, not accompanied by sufficient intake of nutrients would lead to muscle loss and nutritional deficiencies. That is the reason, "Essential nutrient" supplementation should be taken care of.

When integrated with behavioural support and counselling, structured very-low-calorie diets, typically 800–1,000 kcal/day utilizing high-protein foods and meal replacement products, may increase the pace and/or magnitude of initial weight loss and glycaemic improvements compared with standard behavioural interventions.[11]

General recommendations that could be given to decrease energy intake and assure diet quality include:

▶Avoiding food having high proportion of starches, sugars or fat e.g. white flour chapatti, bread, rice, baked products, fried products, high-fat curries, ice creams, sweet drinks and sweets.

▶Limiting intake of very sweet and starchy fruits and vegetables.

▶Increasing intake of salad vegetables, water and high fibre foods.

b) Physical Activity

Regular activity is a key part of managing diabetes. In addition to increasing energy expenditure, it increases insulin sensitivity. Identifying factors that could motivate physical activity and exploring opportunities that can facilitate physical activity are the keys to sustainable physical activity programme. For otherwise healthy people, recommending 30 minutes of brisk walking on most days of the week is appropriate. However, in people having restrictive health conditions or cultural limitations, suggesting other activities that are feasible and enjoyable for them has greater chances of long-term compliance. Use of pedometers and heart rate monitors where feasible can help in observing compliance and safety of exercise programme. (Refer to chapter on physical Activity).

c) Behavioural therapy

Behavioural changes that create an energy deficit, regardless of macronutrient composition, will result in weight loss. Dietary recommendations should be individualized to the patient's preferences and nutritional needs. Assessing an individual's motivation level, life circumstances, and willingness to implement behavioural changes to achieve weight loss should be considered along with medical status when weight loss interventions are recommended and initiated.[12]

Table-2: Treatment Options for Overweight and Obesity in Type 2 Diabetes BMI (kg/m^2)

Treatment	23.0–24.9	25.0–27.4	≥ 27.5
Diet, physical activity, and behavioural counselling			
Pharmacotherapy			
Metabolic surgery			

2) Pharmacotherapy

All approved medications for weight loss have been shown to improve glycaemic control in patients with type 2 diabetes and delay progression of Prediabetes to Diabetes.[13]

Persons with a body mass index of 25 kg/m2 and type 2 Diabetes who fail to loose weight with diet and activity modifications may consider medication to assist with weight loss.

Drugs approved for long-term treatment of obesity include orlistat, liraglutide 3mg, phentermine/topiramate, naltrexone/bupropion and Semaglutide 2.4mg.

In Pakistan Currently available drugs include Orlistat, liraglutide and Semaglutide.

Orlistat, a reversible inhibitor of gastrointestinal enzyme lipase, is a common first choice for therapy because of its long history and lack of systemic effects due to limited absorption. It is taken as a 60- to 120-mg capsule three times per day during or up to one hour after a fat-containing meal. Patients should take a daily multi-

vitamin containing fat-soluble vitamins while using orlistat. Gastrointestinal symptoms such as oily stools, flatus, faecal urgency, and faecal incontinence are the most common adverse effects limiting long-term use. These symptoms are more severe in patients consuming greater than the recommended dietary fat intake (30% of total calories).

Liraglutide and Semaglutide are glucagon-like peptide-1 receptor agonists that is administered subcutaneously and leads to weight loss when used for diabetes. Liraglutide dosing for weight loss starts at 0.6 mg per day and is increased in weekly intervals to the full dosage of 3 mg per day. Semaglutide starting dose is 0.25mg weekly which is then gradually increased to 2.4mg weekly. It is one of the strongest weight loss medications of all.

Both may affect the absorption of other medications via delayed gastric emptying. GLP1 agonists are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 syndrome.[14,15]

If a patient's response to weight loss medication is effective (typically defined as >5% weight loss after 3 months of use), further weight loss is likely with continued use. When early response is insufficient (typically <5% weight loss after 3 months use) or if there are significant safety or tolerability issues, consider discontinuation of the medication and evaluate alternative medications or treatment approaches.[16]

Medical devices for weight loss:Since 2015 several minimally invasive medical devices have been approved for short-term weight loss, including gastric balloons, vagus nerve stimulator, and gastric aspiration therapy.[17]

Recently, an oral hydrogel has been approved for long-term use in those with BMI ≥25 kg/m2 to simulate the space-occupying effect of implantable gastric balloons. Taken with water 30 min before meals, the hydrogel expands to fill a portion of the stomach volume to help decrease food intake during meals. The average weight loss is relatively small though. (2–3% greater than placebo).[18]

3) Metabolic Surgery

Patients who have been unsuccessful with extensive lifestyle and medical therapy and who meet criteria for operative intervention based on BMI should be referred for a surgical evaluation.

Metabolic surgery has proven itself to be superior in almost all aspects of Diabetes complication prevention whether its glycaemic control or reduction of cardiovascular risk compared with nonsurgical intervention.[19]

Metabolic surgery should be a recommended option to treat type 2 diabetes in screened surgical candidates with BMI ≥ 37.5 kg/m2 and in adults with BMI 32.5–37.4 kg/m^2 who do not achieve durable weight loss and improvement in comorbidities (including hyperglycaemia) with nonsurgical methods.

Metabolic surgery may be considered as an option to treat type 2 diabetes in adults with BMI 27.5–32.4 kg/m^2 who do not achieve the same with nonsurgical methods.

Metabolic surgery procedures: The most common metabolic surgery procedures are:

▶Gastric bypass,

▶Sleeve gastrectomy,

▶Adjustable gastric band, and

▶Biliopancreatic diversion with duodenal switch.

Each surgery has its own advantages and disadvantages.

Majority of procedures in Pakistan are vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB). Both procedures result in an anatomically smaller stomach pouch and often robust changes in entero-endocrine hormones.

Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, which randomized 150 participants with uncontrolled diabetes to receive either metabolic surgery or medical treatment, found that 29% of those treated with RYGB and 23% treated with VSG achieved A1C of 6.0% or lower after 5 years.[20]

Complications

Major complications occur in 2–6% of those undergoing metabolic surgery including anaesthesia-related risks, dilation of oesophagus, infection and obstruction of stomach.

Minor complications are much more common including vitamin and mineral deficiencies, anaemia, osteoporosis, dumping syndrome, and severe hypoglycaemia.[21]

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CHAPTER 6

Acute emergencies in type 2 diabetes

HYPOGLYCAEMIA:

Hypoglycaemia is always the major concern while deciding about the treatment strategy and fixing glycaemic targets in the management of diabetes.

▶Level 1 or mild hypoglycaemia is defined as a measurable glucose concentration of <70 mg/dL. A blood glucose concentration of 70 mg/dL is a threshold for sympathetic responses like trembling, palpitation, sweating, anxiety and hunger in people without diabetes. Because many people with diabetes demonstrate impaired counter regulatory responses to hypoglycaemia, a measured glucose level of <70 mg/dL is considered clinically important.

▶Level 2 hypoglycaemia or moderate hypoglycaemia is defined as a blood glucose concentration <54 mg/dL, is the threshold for neuroglycopenic symptoms like confusion, weakness, drowsiness, changes in the vision and difficulty in concentration and requires immediate action.

▶Level 3 hypoglycaemia also called severe hypoglycaemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.[1]

In type 2 diabetes, severe hypoglycaemia is associated with reduced cognitive function, and those with poor cognitive function have more severe hypoglycaemia.[2,3]

Severe hypoglycaemia is also a potent marker of high absolute risk of cardiovascular event and mortality.[4]

Table-1: classification of Hypoglycaemia Glycaemic Criteria

Level 1	Glucose <70 mg/dL and ≥54 mg/dL
Level 2	Glucose <54 mg/dL
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia

Reprinted from Agiostratidou et al. [1].

Hypoglycaemic unawareness:

If a patient has level 2 hypoglycaemia without adrenergic or neuroglycopenic symptoms, they likely have hypoglycaemia unawareness.

Sometimes people with diabetes treated with insulin or insulin secretagogues lose their ability to identify hypoglycaemia, a condition known as hypoglycaemic unawareness. This is due to repeated hypoglycaemic episodes that reprogramme trigger centre for release of stress hormones at even lower blood glucose level.

Hypoglycaemic unawareness can be managed by keeping the blood glucose above the desired range for few weeks to avoid hypoglycaemic events. Frequent monitoring is advised in this condition. Glycaemic targets and selection of glucose lowering drugs needs to be redefined in this setting.[5]

Management of Hypoglycaemia:

Physicians should educate patients for avoiding hypoglycaemia and its management.

Fast-acting carbohydrates should be taken at the hypoglycaemia alert value of 70 mg/dL or symptoms of it, if glucose checking is not possible.[6]

Pure glucose (approximately 15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL, although any form of carbohydrate that contains glucose may be used, like one table spoon of house sugar or honey directly or dissolved in water. Fifteen minutes after treatment, if blood glucose is still low the treatment should be repeated. Once the blood glucose is above 70mg/dl or glucose pattern is trending up on CGM, the individual should consume a meal or snack to prevent recurrence of hypoglycaemia.[7]

Severe episode in an unconscious patient is treated by giving 20-50 ml of 50% dextrose water intravenously in 1-3 minutes.

Added fat prolong the acute glycaemic response. In type 2 diabetes, ingested protein may increase insulin response without increasing plasma glucose concentrations.[8] Therefore high protein containing food should be avoided.

Glucagon, if available should be prescribed to all individuals at increased risk of level 2 or 3 hypoglycaemia, so that it is readily available when needed.

Hyperosmolar Hyperglycaemic State (HHS):

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

HHS is associated with higher morbidity and mortality. Therefore it should be diagnosed and managed promptly and intensively.[9,10]

The pathogenesis of HHS is not well understood. Although relative insulin deficiency is present in HHS, endogenous insulin secretion appears to be greater than in DKA, where it is absent.

Insulin levels and sensitivity in HHS are inadequate to facilitate glucose utilisation by insulin sensitive tissues but adequate to prevent lipolysis and subsequent ketogenesis.[11]

Diagnosis
History and physical examination

The process of HHS usually evolves over several days to weeks, and the classical clinical picture includes a history of polyuria, polydipsia, vomiting, dehydration and mental status change. Physical findings may include poor skin turgor, tachycardia, and hypotension. Mental status can vary from full alertness to coma. Focal neurologic signs (hemianopia and hemiparesis) and seizures may also be present.[12] Although infection is a common precipitating factor patients can be normothermic or even hypothermic primarily because of peripheral vasodilation.

Laboratory findings:

Severe hyperglycaemia and dehydration with altered mental status in the absence of significant acidosis and ketosis is hallmark of HHS.

Key Differentiating points between DKA and HHS has been highlighted in table 2:

Table-2: DKA vs HHS - LAB FINDINGS / DKA / HHS

Plasma Glucose (mg/dl)	>250	>600
Arterial pH	<7.3	>7.3
Serum Bicarbonate(mEq/l)	≤18	>18
Urine Ketone	Positive	Small
Serum Ketone	Positive	Small
Effective serum osmolality	Variable	>320mOsm/kg
Anion Gap	>12	Variable
Mental status	Alert to Coma	Stupor/Coma

Management

Successful management of HHS requires correction of dehydration, blood glucose, electrolyte imbalances and most importantly identification of precipitating factors.9

1) Fluid therapy: In the absence of cardiac compromise, isotonic saline (0.9% NaCl) is infused at a rate of 15–20 ml/kg body weight in the first hour or continue till severe hypovolaemia is recovered. In case of mild dehydration and normal/high serum sodium shift to half saline at a rate of 250 to 500ml/h from second hour. Shift to 5% Dextrose with 0.45% Saline at a rate of 150 to 250ml/h once blood glucose is 300mg/dl.

2) Insulin Regular: Start IV infusion at 0.14u/kg body weight/h. If blood glucose does not fall by 10% in first hour give 0.14u/kg bolus. Once blood glucose is 300 reduce infusion rate to 0.02 to 0.05u/kg/h. Maintain blood glucose between 200mg/dl to 300mg/dl till patient is mentally alert.

3) Potassium: Give 20 to 30 mEq of Potassium in each liter of fluid to keep serum levels between 4 to 5.

Do not start potassium if urine output is less than 50ml/h or serum potassium is >5.2mEq/l. If serum potassium is less than 3.3, hold the insulin and give 20mEq/h until it is more than 3.3mEq/l.

Check electrolytes, BUN, venous pH, creatinine and Glucose every 2 hour until stable. Initiate subcutaneous insulin once HHS is resolved (normal serum osmolality) and patient is able to eat.

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CHAPTER-7

Hypertension And Diabetes

High blood pressure is recognized as a major risk factor for CVD and CKD.1

Monitoring:

- Blood pressure should be measured at every clinic visit. Patients newly diagnosed with systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg should have blood pressure reading multiple times and confirmed on a subsequent day. Patients with history of cardiovascular disease and blood pressure reading of ≥180/110 mmHg; a single visit is sufficient to diagnose hypertension.[1]
- Domiciliary Blood pressure monitoring is advised for all diabetic patients with Hypertension. On the initial visit orthostatic blood pressure should be checked and may be repeated as indicated.
- Domiciliary blood pressure monitoring and 24 hours ambulatory BP monitoring may give insight on white coat hypertension
- Blood pressure measurement should be measured by trained personnel. Standard protocol for blood pressure measurement must be followed i.e., in the seated position, with feet on the floor and arm supported at heart level, after 5 minutes of rest. Cuff size should be appropriate for the upper arm circumference.[2,3]

Goals (Targets)

- For diabetic patients with hypertension, blood pressure targets should be individualized keeping in mind the potential side effects of drugs, patient preferences and cardiovascular risks.
- For diabetic individuals who have hypertension but no other co morbidities , blood pressure target should be less than 140/90 ; In these individuals with preexisting ASCVD or 10 year ASCVD risk equal to or more than 15% , target BP of less than 130/80 would be more appropriate if it could be achieved safely.[4]
- In pregnant diabetic patients with pre-existing hypertension, a BP target of 110–135/85 mmHg is suggested in order to minimize foetal growth impairment and to reduce the risk of maternal complications.

Therapeutic Management Strategies

- For those patients with BP of more than 120/80 mmHg, Lifestyle intervention should be started in the form of weight loss if required, DASH diet, increase in physical activity, moderation in alcohol consumption, reduction in sodium intake to less than 2300 mg per day (simplest strategy is not to add table salt to meals) , increase in potassium intake, increase in consumption of vegetables and fruits (8 to 10 servings in a day), low fat dairy product (2 to 3 servings in a day).[5]
- Patients with confirmed blood pressure readings of >140/90mmHg should be promptly initiated pharmacological therapy, in addition to dietary changes (e.g. DASH Diet/ low Sodium Intake) and life style modifications. Therapy must be titrated to achieve the desired goals.
- Patients with confirmed blood pressure readings of ≥160/100 mmHg, pharmacotherapy should be promptly initiated and timely titrated to two drugs or a single-pill combination of drugs which have shown in clinical trials to reduce cardiovascular events in patients with diabetes.[6]
- For hypertensive patients with diabetes and coronary artery disease,ACE inhibitor/ARBs should be considered as initial therapy.
- ACE inhibitors or angiotensin receptor blockers are also recommended in patients with diabetes and hypertension with urinary albumin to creatinine ratio ≥300 mg/g creatinine and suggested when it is between 30–299 mg/g creatinine.[7]
- β-Blockers have not shown any reduction in mortality as antihypertensive agent in absence of active angina, history of MI or HfrEF.[8]
- If target blood pressure level is not achieved after 2-3 months, addition of either a dihydropyridine calcium channel blocker or thiazide diuretic may be considered.
- If ACE inhibitors, ARBs, or diuretics are used, serum

creatinine and serum potassium levels should be monitored after 10 days and then at 6th week. Ideally monitor creatinine every six to twelve months if it does not exceed more than 30% from its baseline.[9]

- It is common to have an acute rise in serum creatinine of up to 30% within 2-5 days of initiating an ACEI or ARB, especially if the patient has CKD/CHF. These can be safely continued in these patients if the creatinine subsequently stabilizes at the higher level. Annual monitoring of serum creatinine or estimated glomerular filtration rate and serum potassium should be done in patients using these drugs.
- A blood pressure ≥140/90 mmHg despite of lifestyle modifications plus optimal doses of three antihypertensive drugs including a diuretic is labelled as 'Resistant hypertension'. Before making a diagnosis of resistant hypertension, few conditions like white coat hypertension, non compliance with drugs and secondary hypertension should be kept in mind.
- Mineralocorticoid receptor antagonists have shown to be effective while managing resistant hypertension in patients with diabetes when they are added to existing treatment regimens as they have some additional cardiovascular benefits and help in reduction of proteinuria.[10]
- Safe antihypertensive drugs in pregnancy include methyldopa, nifedipine (long-acting preparation) and labetolol while hydralzine can be considered in settings where rapid control of blood pressure is required in pregnancy or in severe preeclampsia.[11]
- Additionally, antihypertensive effects of other medication such as SGLT 2 inhibitor, GLP Agonist and statins should be taken into account specially when starting them during the same visit.

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CHAPTER 8

Diabetes and dyslipidaemia

Dyslipidaemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. It may be manifested by elevation of the total cholesterol, low density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and/or a decrease in the high-density lipoprotein (HDL) cholesterol concentration in the blood.[1]

Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and results in an estimated $37.3 billion in cardiovascular-related spending per year associated with diabetes .[2]

Dyslipidaemia (particularly high LDL cholesterol and Low HDL) coexisting with type 2 diabetes is a clear risk factor for ASCVD, and diabetes itself confers independent risk. Large number of studies have shown effectiveness of preventing or delaying ASCVD by controlling cardiovascular risk factor that includes dyslipidaemia.

Modifiable cardiovascular disease risk factors in addition to glycaemic control includes weight reduction, smoking cessation, abstinence from alcohol, blood pressure control, lipid management.

Lifestyle modifications specially targetting weight reduction in overweight or obese people, increased physical activity, modification of diet and pharmacological intervention are the mainstay of management of dyslipidaemia.

Diagnosing and Monitoring Dyslipidaemia in Diabetes

- Obtain lipid profile at diagnosis or initial medical evaluation.
- Obtain fasting lipid profile (min 8 hours of fasting) at initiation of statin or other lipid lowering therapy, then 4-12 weeks after initiation or a change in dose and annually thereafter. This strategy may allow better guidance to response to therapy and medication adherence.1,3
- When a health care provider considers that the patient needs to start Statin therapy, it should be maintained lifelong.

Primary Prevention

Statin Therapy

- In addition to lifestyle therapy, use of moderate-intensity statin therapy is recommended in patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease. High intensity statin may be considered in patients with diabetes at higher risk for ASCVD(individuals with multiple cardiovascular disease risk factors).[1,3]
- Goals of Statin therapy is to reduce LDL cholesterol by 50% of baseline or <70mg/dl(1.8mmol/L) in individuals with higher risk of ASCVD.
- Optimization of all modifiable cardiovascular disease risk factors should be done for patients with diabetes aged 20–39 years with or without additional atherosclerotic cardiovascular disease risk factors.
- In selected patients with diabetes aged 20-39 years with additional atherosclerotic risk factors use of moderate intensity statin may be considered in addition to life style intervention. The decision to start statin therapy should be made after an informed discussion between the physician and patient about the risks and benefits of statin therapy.[3]
- All patients with diabetes and atherosclerotic cardiovascular disease should receive high-intensity statin in addition to lifestyle therapy.
- Goals of Statin therapy is to reduce LDL cholesterol <70 mg/dl(1.8mmol/L) in patients with diabetes and atherosclerotic cardiovascular disease.
- If LDL cholesterol is >70 mg/dL on maximally tolerated statin dose in patients with diabetes and atherosclerotic cardiovascular disease, consider adding additional LDL lowering therapy (such as ezetimibe).
- Patients who do not tolerate the recommended intensity statin, the maximally tolerated statin dose should be used.[3]
- Statin therapy is contraindicated in pregnancy.

Managing other lipoprotein fractions of lipids

- Patients with diabetes and moderate hypertriglyceridaemia (150–499 mg/dL), physicians should rely on optimization of life style factors such as dietary modification, increase physical activity and treat secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides.[1,3]
- For patients with diabetes and moderate to severe hypertriglyceridaemia >500 mg/dl despite lifestyle changes and improved glycaemic control, therapy with fibrates should be started. Additional therapeutic options include Omega-3 acid ethyl esters (Fish oil) and Niacin (nicotinic acid) can be used in selected patients with high risk of ASCVD.

Table 8.1 High-intensity and moderate-intensity statin therapy High-intensity statin therapy (lowers LDL cholesterol by >50%)

Atorvastatin 40–80 mg
Rosuvastatin 20–40 mg
Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 10–20 mg
Rosuvastatin 5–10 mg
Simvastatin 20–40 mg
Pravastatin 40–80 mg
Lovastatin 40 mg
Pitavastatin 1–4 mg

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CHAPTER 9

Guidelines On Diabetic Foot And Peripheral Vascular Disease

Diabetic foot lesions are responsible for more hospitalisations than any other complication of diabetes, and is the leading cause of non-traumatic lower extremity amputations worldwide.[1] Around 85% of amputations are preceded by ulcers which are preventable. Identification of feet at risk by appropriate measures can help in preventing diabetic foot ulcers.[2]

Following are some of the recommendations for assessment and management of diabetic feet.

History: A detailed history regarding foot problems should be taken including pain in lower limbs, numbness, paraesthesias, rest pain, intermittent claudication, prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy and renal disease etc. [3]

Examination: A thorough physical examination should be done even in asymptomatic patients.

Warning signs of foot problems:

- Burning or tingling in the feet or painful feet
- Loss of sensation of heat, cold, or touch
- Changes in colour or shape of feet
- Loss of hair on the toes, feet, and lower legs
- Thickening and colour change of the toenails
- Onset of blisters, sores, ulcers, infected corns, or ingrown toenails

Physical examination of the diabetic foot can be divided into following 3 parts:

- Assessment for peripheral neuropathy
- Assessment of vascular insufficiency
- Examination of the ulcer and the general condition of the extremity

***** Assessment of Neuropathy:**

- Assessment of neuropathy can be done with 10 gm monofilament for pressure perception, 128 Hz tuning fork for vibration sense and tactile sensation by cotton wool. Achilles tendon reflex should be examined.
- In more specialized centres, Neurothesiometer can be used to assess vibration perception threshold (VPT).

***** Assessment of vascular insufficiency:**

- Screen for vascular insufficiency by palpating the foot and leg pulses
- Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle-brachial index and or further vascular assessment as appropriate.
- All diabetic patients with non-healing ulcer having ABI <0.9 should be referred to secondary or tertiary centres for further evaluation of PAD by colour duplex ultrasound followed by CT angiography, MR angiography or standard X ray angiography, if required.
- All patients with diabetes and an ischaemic foot ulcer should receive aggressive cardiovascular risk management including support for cessation of smoking, treatment of hypertension, control of glycaemia and prescription of a statin as well as low-dose aspirin or clopidogrel.

Assessment of Diabetic Foot Ulcer: The staging of diabetic foot wounds is based on the depth of soft tissue and osseous involvement.

UT Diabetic Foot Wound Classification System

	Grade			
Stage	**0**	**1**	**2**	**3**
A	Pre or post ulcerative lesion completely epithelialized	Super ficial wound, not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With Ischaemia	With Ischaemia	With Ischaemia	With Ischaemia
D	With infection and Ischaemia	With infection and Ischaemia	With infection and Ischaemia	With infection and Ischaemia

Management of Diabetic Foot ulcer:

Management Depends on the Type of Ulcer.

- If an ulcer is present, classify it as neuropathic (usually plantar surfaces of the feet or areas overlying a bony deformity are common sites), neuro-ischaemic (more frequent on the tips of the toes or the lateral borders of the foot) or ischaemic by history and clinical examination.
- Grading and staging of ulcer can be done using University of Texas classification (UT classification).[4]
- For appropriate assessment, the neuropathic ulcers with callus and necrotic tissue should be debrided as soon as possible. Debridement should not be performed in non-infected ulcers with signs of severe ischaemia.[5]
- Treatment of ulcer includes good metabolic control, off-loading of ulcer site with custom made shoes, debridement and cleaning of all necrotic tissue and antibiotics.
- Daily saline or similar dressings to provide a moist wound environment.
- Antibiotic therapy if osteomyelitis or cellulitis is present.
- Offloading the wound by using appropriate therapeutic footwear.
- Evaluation and correction of peripheral arterial insufficiency.
- Deep ulcers requiring abscess drainage, involving bone or if an ulcer is identified as purely ischaemic, refer to tertiary care centre where foot care facilities are available.

Daily Foot Care: Following points should be emphasized to the patients at each clinic visit.

1. Daily inspection of feet:

- It should be emphasized that feet and toes should be inspected daily looking at the top and the sides of feet, the soles, the heels, and the area in between the toes.
- Hand held mirror should be used to inspect the plantar aspect of feet.
- Doctor should be consulted immediately if sores, redness, cuts, blisters, or bruises are observed.

2. Avoid dryness:

- Wash feet every day in tepid water with mild soap.
- Pat dry gently. Infections tend to develop in moist areas, so make sure to dry well the area between the toes.
- Use any available lotion or oil for dry or rough skin. Do not use lotion between toes.

3. Nail cutting technique:

- Trim toenails after washing the feet, when nails are soft.
- Cut straight across rather than in a curved fashion to help prevent ingrown toenails. Don't cut into the corners. Use an emery board to smoothen the edges. Be careful not to cut toenails too short.
- Toenails can be trimmed by a podiatrist or other health care provider if eye sight of the patient is weak or if nails are thick or yellowed due to fungal infection.

4. Proper Footwear:

- Choose comfortable, well-fitting shoes with plenty of room, especially in the toe box.
- Never buy tight shoes hoping they will stretch.
- Do not wear shoes made out of plastic or other materials that do not breathe. Choose leather, canvas, or suede.
- Avoid pointed-toe and high heels. Wear shoes that can be adjusted with laces, buckles, or Velcro.
- Inspect the inside of shoes every day, looking for tears or bumps that may cause pressure or irritation.
- If neuropathy is present, take off shoes after every five hours to change the pressure points on different areas of feet.
- The use of specialized therapeutic foot wear is recommended for high-risk diabetics, including those with neuropathy, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation.

Category of Peripheral Neuropathy

Category	Characteristics	Frequency
0	No Peripheral neuropathy	Once a year
1	Peripheral neuropathy	Once every 6 months
2	Peripheral neuropathy with peripheral artery disease and/or a foot deformity	Once every 3-6 months
3	Peripheral neuropathy and a history of foot ulcer or lower-extremity amputation	Once every 1-3 months

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CHAPTER 10

Microvascular Complications

Diabetic microvascular complications include:

- Diabetic Nephropathy
- Diabetic Retinopathy
- Diabetic Neuropathy

Diabetic Nephropathy:

Diabetic Nephropathy (DN) is the major cause of End-Stage Renal Disease (ESRD) accounting for more than 50% of patients on renal replacement therapy (RRT).[1] Diabetic Kidney disease occurs in 20-40% patients with diabetes. Patients having both Diabetes and kidney disease are at increased risk of cardiovascular complications with increased mortality.[2]

Screening:

- o Patients with Type 1 Diabetes Mellitus (T1DM) should be screened for DN annually ≥ 5 years after the diagnosis in contrast patients with Type 2 Diabetes Mellitus (T2DM) who should be screened for DN at the time of diagnosis and thereafter annually.
- o Diabetic patient having an estimated glomerular filtration rate (eGFR) 30-60 mL/min/1.73m2 and/or urinary albumin creatinine ratio (UACR) ≥ 300 mg/g cr should be screened 6 monthly[2]
- o Normal UACR ≤ 30 mg/g cr, two of three abnormal UACR are required over the period of 3 to 6 months for labelling a patient to have albuminuria. Following conditions may elevate UACR independent of diabetic nephropathy and include exercise within 24 hours, marked hyperglycaemia, hypertension, infection, fever, urinary tract infection, or menstruation and congestive heart failure.[2]

Treatment:

1. First step is to achieve good glycaemic and blood pressure control to reduce the risk of DN or to slow down the progression of DN.[2]
2. T2DM patient having an eGFR ≥ 25 mL/min/1.73m^2 and UACR ≥ 300 mg/g cr are recommended to be treated with sodium-glucose cotransporter 2 inhibitor (SGLT2i) to reduce diabetic nephropathy progression and for cardiovascular risk benefits. If the above-mentioned patients are unable to tolerate SGLT2i then a nonsteroidal mineralocorticoid receptor antagonist (finerenone) is recommended for use to reduce DN progression and cardiovascular risks. [2]
3. In nonpregnant female and males with diabetes and hypertension use of an ACE inhibitor or angiotensin receptor blocker, is recommended in patient with UACR 30-299 mg/g cr and strongly recommended in patients with UACR ≥ 300 mg/g cr. [2]
4. Use of an ACE inhibitor or angiotensin receptor blocker is not recommended for the primary prevention in normotensive diabetic patients with normal UACR and eGFR. [2]
5. Protein intake should be limited to 0.8 g/kg body weight per day in non-dialysis dependent patients with eGFR ≤ 45 mL/min/1.73m2 and a little higher protein intake is advised in dialysis dependent patients to prevent malnutrition. [2]
6. Refer to nephrologist if the patient is having eGFR ≤ 30 mL/min/1.73m2, rapidly progressing kidney disease, uncertain about the aetiology or having difficulty in management. [2]

Diabetic Retinopathy:

Diabetic retinopathy (DR) is the most common cause of blindness in working age group. Diabetic patients are also having increased risk of glaucoma, cataract and other eye disorders as compared to non-diabetic individuals. Global prevalence of diabetic eye disease is as follows, 35% for any DR, 7% for proliferative DR, 7% for macular oedema, and 10% for sight-threatening diabetic eyes disease (STED).[1]

Screening:

- Patients with Type 1 Diabetes Mellitus (T1DM) should be screened for DR annually ≥ 5 years after the diagnosis as compared with patients with Type 2 Diabetes Mellitus (T2DM), who should be screened for DR at the time of diagnosis and thereafter annually by an ophthalmologist or

optometrist.[3]

- Women who have T1DM or T2DM and planning for pregnancy or are pregnant should be counselled about the risk of development and/or progression of diabetic retinopathy. Their eye examination should be done in pre-pregnancy period; then monitoring done in every trimester and continued till 1 year postpartum. [3]

Treatment:

- Optimize blood pressure, glycaemic and serum lipid control to reduce the risk or slow down the progression of diabetic retinopathy.[3]
- Refer patient to an ophthalmologist with any level of diabetic macular oedema, moderate or worsening non-proliferative diabetic retinopathy.[3]
- Patient with proliferative diabetic retinopathy or in some case severe nonproliferative diabetic retinopathy needs panretinal laser photocoagulation to reduce the risk of vision loss.[3]
- Intravitreous injections of anti-vascular endothelial growth factor (VEGF) are a reasonable alternate to panretinal laser photocoagulation. [3]
- Diabetic macular oedema that involves the foveal center and impairs vision acuity, anti-VEGF is the first line treatment for such cases. [3]
- Macular focal/ grid photocoagulation and intravitreal injections of corticosteroid are reasonable alternates not responding to anti-VEGF or when anti-VEGF be used.[3]
- Aspirin dose not increase the risk of retinal haemorrhage so there is no contraindication to its use as cardioprotective medicine in indicated patients with diabetic retinopathy. [3]

Diabetic Neuropathy:

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations.[3]

Screening:

- Patients with Type 1 Diabetes Mellitus (T1DM) should be assessed for diabetic peripheral neuropathy (DPN) annually ≥ 5 years after the diagnosis as compared with patients with Type 2 Diabetes Mellitus (T2DM) who should be assessed for DPN at the time of diagnosis and thereafter annually.[3]
- For assessment of distal symmetric polyneuropathy, the following steps should be taken:
- A detailed history followed by assessment of small fibre function through temperature and pin prick sensation, large fibre function through vibration sensation (128-Hz tuning fork) and foot at risk of ulceration through proprioceptive sensation (10-g monofilament). [3]
- Sign and symptoms of autonomic neuropathy should be assessed in every patient.
- Diabetic patients with established microvascular complications should be assessed for signs and symptoms of diabetic autonomic neuropathy (DAN).[3]
- **Clinical Manifestation of DAN includes:** [3]
- **Cardiac Autonomic Neuropathy:** Decreased heart rate variability with deep breathing, resting tachycardia (>100 bpm), orthostatic hypotension (a fall in systolic BP >20 mm of Hg or in diastolic BP >10 mm of Hg, upon standing without an appropriate increase in heart rate) and sudden death.
- **Gastrointestinal Autonomic Neuropathy:** Constipation, diarrhoea,faecal incontinence.
- **Genitourinary:** Urinary incontinence, difficulty in micturition, retrograde ejaculation and erectile dysfunction.
- **Other:** sudomotor dysfunction with altered sweating (increased or decreased), hypoglycaemia unawareness and decreased pupillary response to light.

Treatment:

- In T1DM patients, good glycaemic control prevents or delays the development of neuropathy and in T2DM good glycaemic control slows down the progression of neuropathy.
- Pregabalin, duloxetine or gabapentin are recommended first line treatment for neuropathic pain in diabetes.[3]

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