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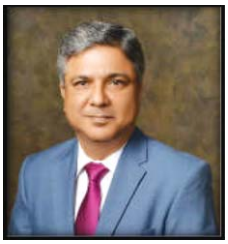

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President's Message

As President of the Pakistan Endocrine Society (PES), I am pleased to share these guidelines with our medical community. These guidelines have been designed keeping in mind our local patient population, their needs and the limitations our healthcare structure faces. The purpose of these guidelines is to have a uniform healthcare delivery protocols across Pakistan for the management of patients with diabetes and cardiometabolic syndrome. These guidelines will help promote better patient care by serving the expanding needs of all healthcare professionals committed to the care of their patients with diabetes. A special emphasis has been placed on preventive practices to avoid not only the disease process itself, but also its complications. Our focus has been on evidence-based medicine and ethical practices. Pakistan Endocrine Society's goal is to enhance our members' knowledge, education, and management skills so that they can provide the highest quality of care to their patients. And with this I hope that you and your patients benefit from it and together we can serve to create healthier, vibrant and productive communities.

Lastly, I am very thankful to the guidelines writing committee members from Pakistan Endocrine Society who all worked very hard to finalize this document.

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PAKISTAN ENDOCRINE SOCIETY (PES) 2020 GUIDELINES FOR MANAGEMENT OF TYPE 2 DIABETES MELLITUS AND CARDIOMETABOLIC SYNDROME

Pakistan ranks 4th in the world with an estimated prevalence of 19.4 million people with diabetes as per IDF data published in 2019.[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 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. (Recommendation) (Table-1).

These guidelines not only concentrate on diagnosis and management of T2DM but also provide a key to maintain referral system from primary to secondary and tertiary care and vice versa. Special emphasis has been given to develop the concept of 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 glycemic control to reduce microvascular and macrovascular complications, but also highlights obesity as 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.

SUMMARY OF RECOMMENDATIONS FOR MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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- Pakistan ranks 4th in the world with an estimated prevalence of 19.4 million people with diabetes as per IDF data published in 2019.[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.

RECOMMENDATION-2: Screening and Diagnosis of T2DM

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

- Fasting plasma glucose: ≥ 126 mg/dl (≥ 7.0 mmol/L) - Fasting defined as no caloric intake for minimal 8 hours, or plasma glucose: ≥ 200 mg/dl (11.1 mmol/L) in the presence of symptoms.
- Plasma glucose 2 hours after 75 gm glucose load ≥ 200 mg/dl (Modified oral glucose tolerance test although not reproducible
- HBA1c value of ≥ 6.5 DCCT (Diabetes control and complication trial) aligned and NGSP (National Glycohemoglobin Standardization Program) certified[5]
- Unless unequivocal symptomatic hyperglycemia is present, the diagnosis should be confirmed by repeat testing on a different day.

2.2- Fasting plasma glucose between 100-125 mg/dl or glucose value 2 hours after 75g OGTT between 140-199 mg/dl (>7.8 to 11 mmol/L) should receive a diagnosis of impaired glucose tolerance (IGT).

Diagnostic Criteria.[3,4]

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

2.3- The above-mentioned tests should be performed in 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: Glycemic Targets &Assessment of Glycemic targets

Recommendation No 3.1: Glycemic Targets:[6]

Sub Category	Fasting blood sugar FBS mg/dl	Random blood sugar RBS mg/dl	Bed time sugar mg/dl	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

Recommendation - 3.2: Assessment of Glycemic targets:

Recommendation - 3.2.1: HbA1c:

- Perform the HbA1C test at least two times a year in patients who have stable glycemic control.
- Perform the HbA1C test quarterly in patients whose therapy has changed or who are not meeting glycemic 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%, maybe advised if this can be achieved without significant hypoglycemia.
- Less stringent A1C goals such as, 8% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing 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 emphasized whenever possible.

- Daily SMBG is superior to less frequent monitoring.
- After achieving target blood glucose SMBG can be done less frequently.
- Monitoring BG before going to bed at night should be done to prevent nocturnal hypoglycemia.

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 alternate day 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):[7]

The key components of lifestyle therapy include:

- Diabetes self-management education (DSME)
- Medical nutrition therapy (MNT) comprising of healthy eating patterns,
- Regular and adequate physical activity,
- Sufficient amount of sleep,
- Smoking cessation with avoidance of all tobacco products.

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 program
- Patients with T2D should be referred to a diabetes education program at the time of diagnosis and the program should be conducted by a trained diabetes educator (where available).
- Set individualized target glycated hemoglobin (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 program 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 normoglycemia, providing adequate calorie intake.
- Simple sugars should be avoided. Food containing complex carbohydrate intake is recommended.

- High dietary fiber and whole grain containing foods should be encouraged.
- Non-calorie sweeteners (aspartame) may be used safely in moderate amounts.
- 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 glycemic 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 min, 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 favored.

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, hyperglycemia, and dyslipidemia 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, gatka, 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, hyperglycemia, and dyslipidemia.
- 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, dyslipidemia, and hypertension.
- Physical activity, diet, and behavioral modification are important components to accomplish weight loss. Additional options for weight loss are medications and bariatric surgery.

RECOMMENDATION 5: Pharmacological Management of Diabetes[18-20]

- Pharmacological therapy should be considered if one fails to achieve glycemic 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 hyperglycemia 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 Glycemic variability or hyper/hypoglycemia 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 hypoglycemic 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:

- Metformin should be prescribed to all patients along with lifestyle modifications, irrespective of their baseline BMI, if there are no contraindications. (E high, R strong).
- If metformin is contraindicated or is not tolerated, GLP1 agonists, SGLT2 inhibitors, DPP4 Inhibitors, sulphonylureas or insulin can be used as alternative.

Recommendation 5.2: Initial Combination Therapy:

- In newly diagnosed people with diabetes presenting with signs and symptoms of hyperglycemia or having HbA1c >8.5%, a second oral agent or insulin should be considered along with metformin. Initial combination of sub maximal doses of antihyperglycemic agents produces better and quicker response than maximum doses of monotherapy.

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 hypoglycemics 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 hypoglycemics and non-insulin injectables 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 hypoglycemia 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 (Hypoglycemia). General rule is 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 (ultralong 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 ultrashort 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 glycemic 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 hypoglycemia as compared to the intensified insulin regimen. 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/hypoglycemia. 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 6.1.1: Monitoring of Blood pressure:

- 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 confirmed on a subsequent day.
- 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 6.1.2: Blood Pressure (Targets):

- Systolic blood pressure (SBP) target should be <140 mmHg and diastolic blood pressure should be <90 mmHg in all people with diabetes and hypertension. There is limited evidence for the benefits of further lowering systolic blood pressure or diastolic blood pressure targets.
- If complications are present (additional risk factors and small vessel disease, particularly albuminuria), a tighter target may be appropriate.

Recommendation 6.1.3: Therapeutic Management Strategies:

- Patients with confirmed blood pressure readings of >140/90mmHg should be promptly initiated pharmacological

therapy, in addition to dietary changes (e.g. DASH Diet/ Sodium Intake) and life style modifications. Therapy must be titrated to achieve the desired goals.

- Lifestyle modifications consists of reducing excess body weight, increasing consumption of fruits and vegetables (4-5 servings per day), consuming low-fat dairy products (2-3 servings per day) and increasing activity levels.
- Sodium intake is restricted, the restriction should be the same for people with and without diabetes. The simplest strategy is not to add table salt to meals.
- For patients with diabetes and hypertension, 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 calcium channel blocker, β-blocker or thiazide diuretic may be considered.
- Initial combination therapy may be needed when SBP is >20 mmHg and/or DBP is >10 mmHg above target, but this may vary with ethnicity and age.
- If ACE inhibitors, ARBs, or diuretics are used, serum creatinine and serum potassium levels should be monitored after10 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.
- 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.
- If blood pressure remains uncontrolled despite good compliance to optimal doses of at least three antihypertensive agents of different class, one of which should be a diuretic, an evaluation for secondary hypertension should be considered.
- 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 same visit.

RECOMMENDATION - 7: Dyslipidemia 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 dyslipidemia.
- **Recommendation 7.3:** All patients with type 2 diabetes over the age of 40 years or below if they have an additional cardiovascular risk factor should receive statin therapy and up-titrated to reach an LDL cholesterol target <70 mg/dL (1.8 mmol/L), despite any level of baseline LDL, unless a very clear risk is identified to withhold the therapy.
- **Recommendation 7.4:** All people with T2D and without established CVD who are ≥ 40 years old and have LDL cholesterol >100 mg/dL (2.6 mmol/L), should start treatment with a statin (primary prevention).
- **Recommendation 7.5:** 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.
- **Recommendation 7.6:** Target LDL cholesterol to be lowered by 50 percent of the baseline or less than 100mg/dl. In patients with atherosclerotic cardiovascular disease risk factors LDL cholesterol target <70 mg/dl is advisable.
- **Recommendation 7.7:** If triglycerides are high, more than 150mg/dl but less than 500mg/dl, strict lifestyle modifications, glycemic 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 glycemic 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:** Low dose aspirin therapy is an option in people with diabetes with increased CVD risk (Primary prevention). This includes family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria and age more than 50 years.
- **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 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. If retinopathy is present, frequency of examination should be suggested by ophthalmologist.
- Aspirin can safely be prescribed in patients with retinopathy as it does not increase the chances of retinal hemorrhage unless there is some other contraindication.

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
- Persistent albuminuria requires treatment with an ACE inhibitor or an ARB even in normotensive people after taking baseline serum creatinine and potassium.

- For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist 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 anti hypertensives are ACEI or ARBs. Combination of these drugs with each other should be avoided due to increased incidence of hyperkalemia
- In selected high-risk patient, 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.
- Dietary proteins should be restricted to 0.8mg/kg / day if macroalbuminuria is present
- People should be referred to a nephrologist when they have DKD stage 4 or 5 (eGFR<30 mL/min/1.73 m2) or unexplained heavy proteinuria with or without hematuria 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
- Medication 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, vit B12 deficiency, Renal disease, Vasculitis, thyroid disease, vitamin D Deficiency, neurotoxic medications, chronic inflammatory demyelinating neuropathy etc., by obtaining relevant tests.
- Take history 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, orthopnea, paroxysmal nocturnal dyspnea etc.)
- Assess cardiovascular risk factors in all T2DM patients annually (Hypertension, dyslipidemia, smoking, obesity, family history of premature CVD etc.). Special attention should be paid to patient presenting with microvascular complication 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 centers for further evaluation of PAD by color duplex ultrasound followed by CT angiography, MR angiography or standard X-ray angiography, if required.
- All patients with diabetes and an ischemic foot ulcer should receive aggressive cardiovascular risk management including support for cessation of smoking, treatment of hypertension, control of hyperglycemia and prescription of a statin as well as low-dose aspirin or clopidogrel.
- Consider reevaluating 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, pre ulcerative signs, improper hygiene or foot wear.
- History of claudication or rest pain in lower limb should be taken. Inspect for color, temperature or edema. 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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DETAILED RECOMMENDATIONS FOR MANAGEMENT OF TYPE 2 DM

INTRODUCTION

Definition:

Diabetes is a complex metabolic disorder characterized by hyperglycemia 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 centered 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 co-morbidities, degree of hyperglycemia, 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 hypoglycemia 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.

CHAPTER-1
REFERRAL CRITERIA FOR DIFFERENT LEVELS OF CARE

1.1: Primary Care

Primary 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 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 as appropriate may be. 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 hypoglycemia, 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 to an endocrinologist or diabetologist or district medical specialist those patients with poor metabolic control as well as those who have 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 T2D with strong family history (MODY?), rapid failure to oral glucose lowering drugs (LADA?) or atypical features suggestive of another endocrinopathy (e.g., Cushing's syndrome, Conn's syndrome, pheochromocytoma and acromegaly).

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 centers.

4. The patients should be referred for a comprehensive eye examination by an ophthalmologist on 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, ischemic 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 is a university-based teaching hospital comprising of an outpatient and inpatient integrated care along with research and education programs. 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, orthopedic surgery, vascular surgery, gynecology 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 centers.

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CHAPTER-2
DIAGNOSIS AND MONITORING OF DM

Classification:

- Diabetes can be classified into four clinical categories:
- Type1 diabetes - occurs due to β-cell destruction, usually leading to absolute insulin deficiency.
- Type2 diabetes - occurring due to a progressive insulin secretory defect and insulin resistance.
- Gestational diabetes mellitus (GDM) - diabetes diagnosed during pregnancy.
- Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug-or chemical-induced diabetes such as during the treatment of HIV/AIDS or drug treatment after organ transplantation.

Diagnostic Criteria:

- DM is a biochemical diagnosis based on fasting and postprandial (2h) glucose levels.
- Diabetes can be diagnosed on the basis of any of the following World Health Organization (WHO) criteria
- Fasting plasma glucose: ≥126 mg/dl (≥7.0 mmol/L) - Fasting defined as no caloric intake for minimal 8 hours, or
- Random plasma glucose: ≥200 mg/dl (11.1 mmol/l) in the presence of symptoms of [1,2,4,8] or
- Plasma glucose after 75 gm glucose load ≥ 200 mg/dl (11.1mmol/l) (Table-1) (Modified oral glucose tolerance test)
- HBA1c value of ≥ 6.5 DCCT (Diabetes control and complication trial) aligned and NGSP (National Glycohemoglobin Standardization Program) certified

Diagnostic Criteria

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

Assessment of the newly diagnosed T2DM patient:

History:

Acute or insidious onset, family history of diabetes, presence of other autoimmune diseases, ethnic origin.

Examination:

- Height, Weight, BMI,
- Pulse including peripheral pulses, Blood pressure,
- Assessment of neuropathy Monofilament, Reflexes, vibration perception,

- Foot examination- including vascular status -----
- Visual acuity, Fundoscopy
- Acanthosis nigricans.

Investigations:

- HbA1c;
- Renal, liver, and thyroid Function;
- Lipid profile;
- Urine for microalbumin;
- Urine DR.
- ECG

Glycemic Targets

Sub Category	Fasting blood sugar FBS mg/dl	Random blood sugar RBS mg/dl	Bed time sugar mg/dl	HbA1c %
Recent/without complications	80-120	80-160	100-140	6.5-7.0
With CCF*, CKD†, CLD‡, Autonomic Neuropathy	100-140	120-180	120-180	7.0-7.5

Assessment of Glycemic targets:

HbA1C:

- Assessment of HbA1C reflects average glycemia over past 3 months. The test is the major tool for assessing glycemic control and has strong predictive value for diabetes complications.[1,2] However, it should be performed from a reliable laboratory.
- HbA1C testing should be performed routinely in all patients with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained.
- The frequency of HbA1 C testing should depend on the clinical situation, the treatment regimen, and the clinician's judgment.
- Perform the HbA1C test at least two times a year in patients who have stable glycemic control).
- Perform the HbA1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals.
- For most non pregnant T2DM patients a reasonable HbA1C goal is 7%.[3]
- For selected individual patients more stringent HbA1C goals such as, 6.5% maybe advised if this can be achieved

without significant hypoglycemia or other adverse effects of treatment. (short duration of diabetes, type2 diabetes treated with lifestyle or metformin only, long life expectancy or absence of advanced cardiovascular disease).

- Less stringent HbA C goals such as, 8% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes.

Self-Monitoring of Blood Glucose (SMBG):

For many people with diabetes, glucose monitoring is key for the achievement of glycemic targets.4 SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. It can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, and adjusting insulin doses. Frequency and timing of SMBG may be guided by patient's specific needs and goals.

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

- Daily SMBG is superior to less frequent monitoring.
- After achieving target blood glucose SMBG can be done less frequently.
- Monitoring BG before going to bed at night should be done to prevent nocturnal hypoglycemia.

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 alternate day until target blood glucose levels are 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.

Continuous Glucose Monitoring (CGM):

In recent years, CGM has emerged as a complementary method for the assessment of glucose levels. Although not widely available in Pakistan because of cost, the introduction of CGM in clinical practice has started and may help a significant number of patients.

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CHAPTER-3
NON-PHARMACOLOGICAL MANAGEMENT OF DIABETES

Lifestyle Modifications (LSM):

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 glycemic 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] 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 hypoglycemia.[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 hemoglobin (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 his doctor on his next visit. This is one of the most important information for health care provider, because based on this record, he will modify the medicine accordingly, meticulously.
- When starting insulin therapy, employ a structured training program with active dose titration.

Following points should specially be emphasized;

3.1.1: Hypoglycemia

Hypoglycemia is defined as blood glucose level less than 70 mg/dl6 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 hypoglycemia 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, behavior 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 hypoglycemia and know the immediate actions required to correct this condition (see chapter on acute diabetic emergencies).

3.1.2: Hyperglycemia:

High blood glucose levels can lead to acute complications like hyperosmolar hyperglycemic state, lactic acidosis or even DKA, or chronic micro or macro vascular complications. Regular blood glucose testing is helpful as patients often do not feel 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 hyperglycemia. 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 behavior is essential to correctly diagnose the reason. Self-monitoring of blood glucose should be emphasized and possible intensification of medicines or insulin may be 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, diarrhea, 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 hyperglycemia, 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.
- Emphasize 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-fiber breakfast, and not skipping meals, to lessen the risk of unhealthy eating late at night.

Physician Delivered Nutrition Therapy Algorithm

A physician delivered nutrition counseling algorithm shown to be effective in primary care settings includes five steps:

a. Address the agenda to the patient to clarify need for nutrition counseling.

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:

1. 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]

2. Intake of fish, skimmed milk and yogurt, green leafy vegetables, should be encouraged to increase nutrient density of diets.

3. Each meal should have food from several food groups particularly, high protein food, fresh or lightly cooked vegetables and fruits

4. 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:

1. 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 normoglycemia and preventing hyperphagia in persons having insulin resistance and hyperinsulinemia.

D. Energy and nutrients:

1. 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 glycemic control, 30 kcal/kg IBW was more acceptable energy level for obese person with diabetes.[8]

2. Protein:

- Adequate protein intake is important for controlling metabolic derangements, attaining normoglycemia, 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.

3. 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 glycemic 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 individualized 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 form of rice and roti gradually to reduce their weight and improve their glycemic control.
- Carbohydrate intake (fruits, milk, yogurt and starchy food) ideally should not be consumed together.
- Consistency in carbohydrate intake results in improved glycemic 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 hypoglycemia. 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

specially 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 glycemic 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 glycemic 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 hypoglycemic 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 hypoglycemia and its management. People requiring insulin or those on potent hypoglycemic agents need to be aware of potential delayed hypoglycemia 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

favored.

- 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, hyperglycemia, and dyslipidemia 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, glycemic status, risk of hypoglycemia, 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 hypoglycemic 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 should 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 alternatives.[3]
- In newly diagnosed patients with T2DM presenting with signs and symptoms of hyperglycemia 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 antihyperglycemic agents produces better and quicker response than maximum doses of monotherapy.[3-5]

Factors Influencing Management Strategies

CLINICAL FACTORS

- Age
- Weight
- Degree of hyperglycemia
- Risk of hypoglycemia / hypoglycemia unawareness
- Presence of any co-morbidity/ complication
- Socio-economic status
- Individual preference

PHARMACOLOGICAL FACTORS

- Efficacy in glycemic control
- Risk of hypoglycemia
- Risk of weight gain

- Drug interactions
- Side effects
- Cost and availability
- Cardiovascular benefits.
- Renal benefits

RATIONALE AND EVIDENCE

Available Therapeutic Agents in Pakistan

Metformin

- Metformin is currently the drug of first choice for the treatment of hyperglycemia in DM, without stimulating insulin secretion, promoting weight gain, or causing hypoglycemia.[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%.[6]
- It also provides benefits of weight stability or slight weight reduction.[7]
- It is generally well tolerated. Most commonly reported side effects are anorexia, nausea, diarrhea and a metallic taste. These effects can be minimized if metformin is taken with meals.
- Lactic acidosis is the only serious side effect. However, its risk incidence is extremely low.[8]
- It is contraindicated in CKD Stage 4 and 5 (eGFR<30).9 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 by 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 glycemic targets are achieved or another oral agent is added in regime.
- It may also be associated with Vit B12 deficiency in some cases with long term use.
- The maximum dose is up to 2550 mg in divided doses. It should be started at a low dose, typically 500mg twice daily, with upward titration if desirable control of hyperglycemia is not achieved. The drug is well tolerated.

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%.[10] Available SGLT2 agents in Pakistan are dapagliflozin (5 and 10 mg) and empagliflozin (10 and 25 mg).
- 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.
- The main side effects are increased incidence of genital mycotic infections and urinary tract infections.
- Efficacy of SGLT2i is decreased in chronic kidney disease and is contraindicated in patients with eGFR less than <30.[2,3,10]

GLP 1 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 glycemic control, reduce patient weight and improve patient-reported outcomes when administered as monotherapy or add-on therapy to other glucose-lowering drugs.
- GLP-1RAs reduce, or at least not increase, the risk of major cardiovascular events.
- GLP-1RAs are generally well tolerated with a very low intrinsic risk of hypoglycemia.
- 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.[11,12]
- 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) and Dulaglutide (1.5mg single dose pen, taken once weekly).

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.[13]
- Lower HbA1c by approximately 0.5-1.0% and are weight neutral.[13,14]
- Proven efficacy when combined with metformin, sulfonylurea or both metformin and sulfonylurea.
- Low risk of hypoglycemia.
- Recent cardiovascular studies have shown that these agents do not increase the CV risk.[13,14]

Sulphonylureas (SU)

- SUs reduces plasma glucose levels by enhancing insulin secretion, with an average A1c reduction of 1.5%.[15]
- The major adverse side effect is hypoglycemia. The risk is higher in renal impairment, liver cirrhosis and in the elderly. Weight gain is also a common side effect.[13]
- Second generation SUs (gliclazide, glimepiride) have a lower risk of hypoglycemia 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 hypoglycemia.

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 hyperglycemia.
- Can reduce HbA1c by 0.2%.[16]
- 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 edema, weight gain, risk of congestive heart failure (CHF) and increased risk of fractures. This significantly limits their clinical use.[17]
- Have conflicting findings regarding myocardial infarction (MI) risk. However, they should not be used in NYHA class 2 patients.[2,3,17]
- Inconclusive evidence for their association with bladder cancer.[17]
- 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.[18]
- The main risk is hypoglycemia and weight gain.
- Mainly excreted through hepatic route, hence is safe in renal compromised patients.[18]

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 glycemic targets with lifestyle modification (diet and exercise) or with a maximum dose of oral hypoglycemics or noninsulin injectables, e.g. Glucagon like peptide-1 (GLP-1) receptor agonist
- Unable to tolerate oral hypoglycemics or non-insulin injectables.
- Being treated for acute complications of diabetes (DKA, HHS).
- Undergoing surgery.
- Unable to use oral hypoglycemics 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).[19,20]

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 timely correction of hypoglycemia has been imparted.
- Different types of insulin and their duration of action are discussed in the table given below

How to initiate insulin in people with T2DM?

If Fasting Blood Glucose Levels are High:

- Oral hypoglycemic agents can be used to control blood glucose levels in combination with basal insulin.[2,3,19]
- A single dose of intermediate-acting insulin NPH or long-acting insulin Glargine U-100 or Detemir can be added at

bedtime with the current oral therapy.[18,19]

- To prevent hypoglycemia, it is advised to initiate insulin with a starting dose of 0.2 units/kg, while adjusting the dose by increasing 2 units every 3 days based on the fasting blood glucose levels until the desired target is achieved.[18,19]
- 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.[19,20]

If only Post-Prandial Blood Glucose Levels are High:

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 glycemic levels requiring higher insulin doses, and may reduce the amount of insulin required in these patients.[20]
- 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 2 units every 3 days until the desired target is achieved.[21]
- Add once daily dose of Degludec+Aspart (70/30) 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 hypoglycemia 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.[21]

Example of Intensive insulin regimen by using rapid acting insulin or intermediate or long acting insulin in 70 kg man with type 1 diabetes. Assume he is consuming 75g carbohydrate at breakfast, 60g at lunch, and 90g at dinner.

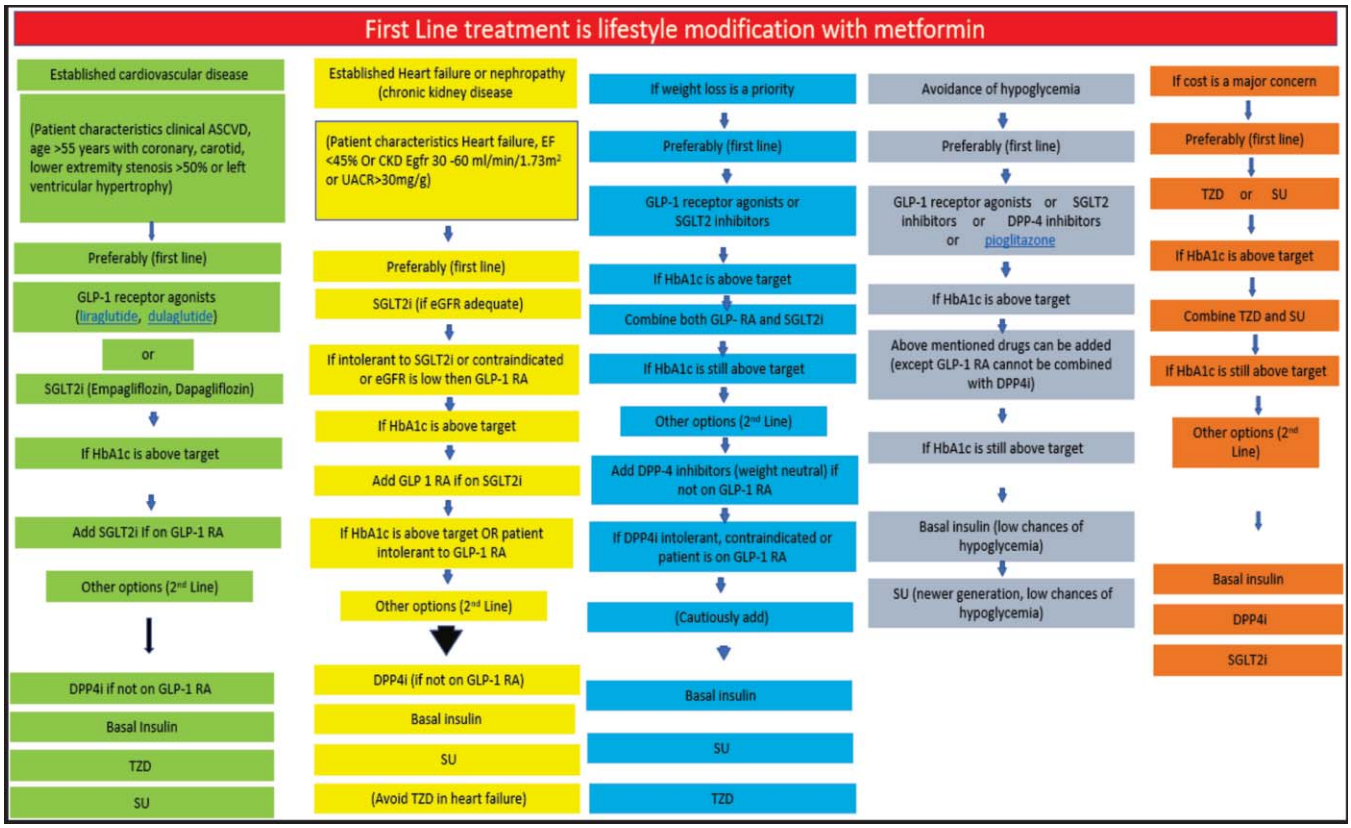
Insulin	Pre breakfast	Pre lunch	Pre dinner	Bed time
Rapid acting insulin analog lispro, aspart, glulisine	6U	4U	6U	___
NPH	12U	0U	8U	
OR				
Rapid acting insulin analog	5U	4U	6U	___
Insulin glargine OR degludec OR	___	___	___	16U
Insulin detemir		___	___	16 U

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

Table: Insulin Commercially Available in Pakistan			
Type of Insulin	**Brand Name**	**Manufacturer**	**Dosage form**
Ultra-short acting/ Rapid-acting Insulin analogs (Bolus)			
Lispro	**Humalog**	**Eli Lilly**	Vial/Cartridge/Pen
Aspart	**NovoRapid**	**Novo Nordisk**	Vial/Cartridge/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/Cartridge
	Insuget-R	**Getz Pharma**	Vial
	Innogen-R	**Pharm Evo**	Vial
Intermediate-acting Insulin (Basal)			
NPH (Neutral Protamine Hagedorn)	**Humulin-N**	**Eli Lilly**	Vial
	Insulatard	**Novo Nordisk**	Vial/Cartridge
	Insuget-N	**Getz Pharma**	Vial
	Innogen-N	**Pharm Evo**	Vial
Long-acting Insulin Analogs (Basal)			
Insulin Glargine (U-100)	**Lantus**	**Sanofi Aventis**	Vial/Pre-filled pen
Insulin Detemir	**Levemir**	**Novo Nordisk**	Pre-filled pen
Ultra-Long acting Insulin Analogs (Basal)			
Insulin Glargine (U-300)	**Toujeo (1.5)** **Toujeo Max (3 ml)**	**Sanofi Aventis**	Pre-filled pen
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
	Innogen 70/30	**Pharm Evo**	Vial
Pre-mixed Analogs [NPL (Neutral ProtamineLispro) + Lispro (Ultra-short acting Analog)]			

NPL + Lispro	**Humalog Mix 25**	**Eli Lilly**	KwikPen/Cartridge
	Humalog Mix 50	**Eli Lilly**	
Pre-mixed Analogs [70% Insulin Aspart Protamine + 30% Insulin Aspart (Ultra- short acting Analog)]			
Aspart Protamine + Aspart	**Novo Mix 30**	**Novo Nordisk**	FlexPen
	Novo Mix 50		
Pre-mixed Ultra-long acting and Ultra-short acting Analogs (70% Insulin Degludec and 30% Insulin Aspart)			
Degludec + Aspart	**Ryzodeg**	**Novo Nordisk**	Flex Pen
Insulin+GLP-1 combination			
Xultrophy	3.6mg Liraglutide/ml	100U degludec/ml	

Table : Insulin Pharmacodynamics					
Type of Insulin	**Onset**	**Peak**	**Effective Duration**	**Meal Relation**	**Color**
Ultra-short acting/ Rapid-acting Insulin analogs (Bolus)					
Lispro Aspart Glulisine	< 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	0.5-1 Hr	2-3 Hrs	3-6 Hrs	30-45 mins before meal	Clear
Intermediate-acting Insulin (Basal)					
NPH	2-4 Hrs	4-10 Hrs	10-16 Hrs	Not related with meal. Once, twice or thrice daily (6)	Cloudy
Long-acting Insulin Analogs (Basal)					
Insulin Detemir	0.8-2 Hrs (Dose Dependent)	Relatively 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	Relatively Flat	20-24 Hrs		
Ultra-Long acting Insulin Analogs (Basal)					
Insulin Glargine (U-300)	2-4 Hr	Relatively Flat	>24 Hrs	Not related to meal. Once daily - Morning or Evening.	Clear
Pre-mixed 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
Pre-mixed Analogs [NPL (Neutral ProtamineLispro) + Lispro (Ultra-short acting Analog)]					
NPL + Lispro	< 15 Min	Dual	10-16 Hrs	15 min or just before/ after meal	Cloudy
Pre-mixed Analogs [70% Insulin Aspart Protamine + 30% Insulin Aspart (Ultra- short acting Analog)]					
Aspart Protamine + Aspart	<15 Min	Dual	15-18 Hrs	15 min or just before/ after meal. Can be given once, twice or thrice daily (7,8)	Cloudy
Pre-mixed Ultra-long acting and Ultra-short acting Analogs (70% Insulin Degludec and 30% Insulin Aspart)					
Degludec + Aspart	< 15 mins	Dual	>24 Hrs	15 min or just before/ after meal	Clear



Insulin Initiation

Visit 1

Discuss need for insulin, including barriers to overcome
Review barriers. Adjust oral anti-diabetics Home BG testing for 2-4 wk., glucose log book

Visit 2

Review log book. Prescribe insulin. Demonstrate/teach use of insulin pen. Resources. Handouts on injection sites, dealing with low Blood Sugar, diet counselling

Visit 3

Review injection technique, review log, adjust insulin dose, Address patient concerns

Insulin Initiation

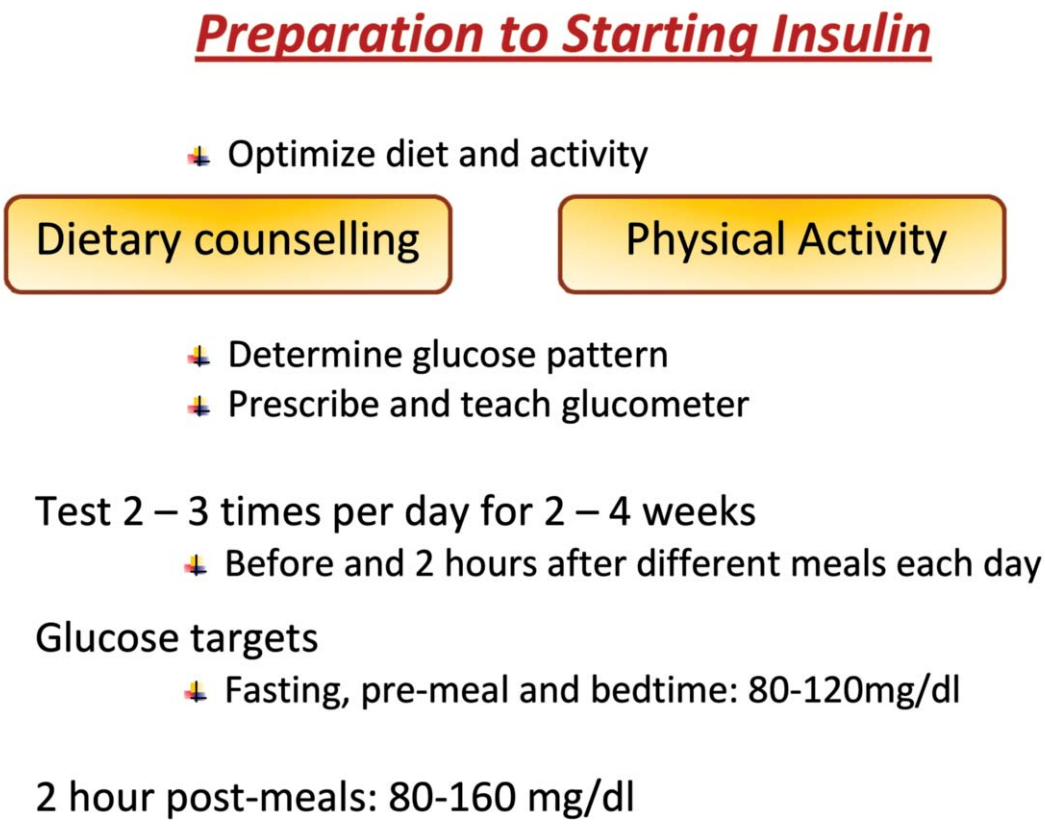
Insulin may be used at almost any stage of diabetes

In primary care, consider insulin if:

- Using 2 or more oral glucose lowering agents at or near maximal doses
- Diet, activity and medication have been reviewed and modified to minimize contributing factors
- Hyperglycemic Symptoms (wt. loss, polyuria, polydipsia)

AND

- A1C persistently > 8.5% (> 3-6 months) or
- A1C >10% and hyperglycemic symptoms (wt. loss, polyuria, polydipsia)



THREE DIFFERENT OPTIONS FOR INITIATION OF INSULIN

OPTION A

Basal added to Oral Agents	Start Insulin	Titration	Short Term Follow-up (1-4 week)	Long Term Follow-up (After 3 months)
Continue other oral agents initially (until glucose control improves with insulin)	**NPH (Humulin N, Insulatard]** • least expensive, reasonable first choice for most T2DM **Glargine (Lantus)** • less nocturnal hypoglycemia, for patients who are prone to hypoglycemia **Detemir (Levemir)** • less nocturnal hypoglycemia, for patients who are prone to hypoglycemia, less weight gain	• Starting dose: 10-16 units OD at bedtime • Test glucose 1-2 times per day: before breakfast and bedtime • Increase basal insulin by 2 units every 3-5 days until fasting glucose is in target (FBG 80-120mg/dl)	• Fasting glucose still elevated • Continue to increase dose FBG in target - No further increase • A1C in 3 months	• Review A1C and glucose records after 3 months • If A1C above target, consider intensifying insulin

OPTION B

Bolus Insulin with Meals	Titration	Testing & Insulin Adjustment	Short Term Follow-up (1-4 week)	Long Term Follow-up (After 3 months)
Regular (Humulin R, Actrapid) • Lower cost • Should be given 30-40 minutes before a meal • Reasonable first choice for patients with consistent lifestyle, who do not require flexibility in their diet/ activity **Rapid Acting (Aspart [Novorapid], Lispro [Humalog], Glulisine [Apidra])** • Greater cost • Must be given within 10-15 minutes before meal (may be given during or immediately after meal in some cases) • Better choice for patients who desire flexibility in their diet and activity	• Start with 4-6 units before largest meal • Increase by 1 unit every 2-3 days until 2-hr post-meal glucose is in target	• Test glucose 2 hours after meal(s) • Increase bolus insulin by 1 – 2 units every 3 – 5 days until PPG <180 mg/dl	• 2-hour post-meal(s) glucose > 180 mg/dl – increase bolus insulin by 1 – 2 units every 3 – 5 days until PPG < 180 mg/dl	• If post-prandial glucose still elevated, consider increasing bolus doses or refer to endocrinology/ internal medicine

OPTION C

Pre-mixed Insulin	Titration	Testing & Insulin Adjustment	Short Term Follow-up (1-4 week)	Long Term Follow-up (After 3 months)
• Pre-mixed insulins • Human Premix (30/70) • Analogue Premix (Novomix-30, HumalogMix-25, Mix-50)	• Start with major meals at 0.3u/kg/day divided doses Split dose 50/50 or 70/30, depending on largest meal Titrate dose for glucose covered by NPH • Increase 2 units every 2-3 days until target reached	• Test glucose 2 per day: Before Breakfast and Supper • Increase pre-mixed insulin by 2 units every 3-5 days until pre-meal glucose in targetrange	• Pre-mixed Insulin BID • Pre-breakfast glucose elevated – increase supper insulin • Pre-supper glucose elevated – increase breakfast insulin& avoid afternoon snacking	• Review A1C and glucose records after 3 months If A1C above target, consider intensifying insulin • Review diet and activity (more consistency, avoid simple carbs – especially at lunch) • Consider switching to Basal/Bolus (depends on patient)

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

Patient 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 inquired 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) and lipodystrophy (immune mediated disfiguring atrophy of tissues). Insulin in 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. Injection site should be rotated on frequent basis and body area for injection should also be rotated on as needed basis.

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CHAPTER-5
OBESITY AND DIABETES

Key points:

- Obesity is a significant contributor to health problems including Diabetes.
- There is substantial evidence that even modest weight reduction whether through lifestyle/behavioral interventions, weight reducing medicines, or bariatric surgery-can delay the progression from prediabetes to type 2 diabetes and improve glycemic 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]
- Obesity is often multi-factorial, based on both genetic and behavioral factors.
- The primary aim of obesity treatment is to reduce weight-related health risks and improve quality of life. A weight loss of at least 5% has been shown to produce modest improvements in cardiometabolic risk factors.[4]
- Treatment of obesity usually requires more than just dietary changes. It usually requires support and counseling, in addition to dietary modifications and exercise. 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 behavioral interventions.
- Increased physical activity should be recommended for weight loss in combination with diet and behavioral modifications.
- Physicians should consider medications for weight loss in patients with a BMI of 25 kg per m^2 or greater, or 23 kg per m^2 or greater who also have comorbidities and have unsuccessfully tried diet and lifestyle modification first.
- Patients with a BMI ≥ 37.5 kg/m^2 and those with a BMI greater than 32.5-37.4 kg/m^2 who also have obesity-related comorbidities should be referred for consideration of bariatric surgery. Patients with a BMI greater than 30 kg per m^2 who also have obesity-related comorbidities may be candidates for adjustable gastric banding.

Role of Physician's in Screening and Managing Obesity?

Physicians should screen all patients for obesity with measurement of body mass index (BMI) or waist circumference. Diet and behavioral interventions should be initiated in patients who are obese.

Table 1. Weight Classifications.

CLASSIFICATION	BODY MASS INDEX (KG PER M^2)	WAIST CIRCUMFERENCE
Underweight	< 18.5	—
Normal weight	18.5 to 22.9	Male < 40 in (102 cm)
		Female < 35 in (89 cm)
Overweight	23 to 24.9	—
Class 1 obesity	25 to 26.9	Male ≥ 40 in
Class 2 obesity	27 to 29.9	Female ≥ 35 in
Class 3 obesity	≥ 30	

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.

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

2. Medications

3. Bariatric Surgery

DIET

- As far as diet is considered, simple and realistic diet modifications have the highest likelihood of success. Energy intake is reduced by decreasing the intake of fats and/or carbohydrates.
- Regardless of the method chosen for inducing negative energy balance, assurance of nutritionally adequate diet is essential to prevent malnutrition and assure sustainability.
- Negative energy balance, and weight loss, accompanied by insufficient intake of nutrients would lead to muscle loss, nutritional deficiencies and non-compliance. High carbohydrate leads to higher amount of insulin secretion from pancreas. Insulin promotes positive energy balance as it promotes fat synthesis (lipogenesis) and storage and inhibits fat breakdown (lipolysis). A diet that lowers the amount of insulin secretion is beneficial for weight loss.

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 fiber foods.

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 program. 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 program. (Refer to chapter on physical Activity).

MEDICATIONS

Anti-obesity drugs[6,7]

- Medications should be considered only for patients who have not achieved weight loss goals with diet and lifestyle changes, and after an extensive discussion of the risks and benefits.
- Persons with a body mass index of 30 kg per m2 or greater than 27 kg per m^2 with comorbidities who fail in losing weight with diet and activity modifications may consider medication to assist with weight loss. Medications approved for long-term treatment of obesity include orlistat, liraglutide, phentermine/topiramate, and naltrexone/bupropion.
- Despite their indication for long-term therapy, the optimal duration of treatment is unclear; the available evidence was limited to one to two years.
- In Pakistan Currently available drugs include Orlistat and liraglutide.
- 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, fecal urgency, and fecal 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 is a glucagon-like peptide-1 receptor agonist that is administered subcutaneously and leads to weight loss when used for diabetes. 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. It may affect the absorption of other medications via delayed gastric emptying. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 syndrome.[6]

Bariatric 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.

Which Patients Should Be Referred for Bariatric Surgery?

Candidates for bariatric surgery include those with a BMI of 37.5 kg per m^2 or greater, regardless of comorbidities, or a BMI of 32.5 kg per m^2 or greater who have at least one severe obesity-related comorbidity, such as type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, nonalcoholic fatty liver disease, debilitating arthritis, or impaired quality of life.

Bariatric surgery is advisable in those patients who had made reasonable attempts to reduce body weight and demonstrate a commitment to follow post-operative recommendations, maintain necessary lifestyle changes and agree to lifelong post-operative medical surveillance.[8]

- An extensive preoperative assessment of comorbidities and surgical risk, as well as a willingness to comply with the long-term management and follow-up requirements, is crucial.
- Health care physicians should inform and discuss this option with their patients. These patients need a thorough evaluation and a long-term follow-up after surgery to avoid weight regain and malnutrition therefore the selected patients should be referred to a multidisciplinary team including bariatric surgeon.

Bariatric surgical procedures cause weight loss by restricting the amount of food the stomach can hold, causing

malabsorption of nutrients, or by a combination of both gastric restriction and malabsorption. Bariatric procedures also often cause hormonal changes. Most weight loss surgeries today are performed using minimally invasive techniques (laparoscopic surgery).

Bariatric surgery procedures:

The most common bariatric surgery procedures are:

- Gastric bypass,
- Sleeve gastrectomy,
- Adjustable gastric band, and
- Biliopancreatic diversion with duodenal switch.

Each surgery has its own advantages and disadvantages.[9,10] Health benefits of bariatric surgery, determined largely from nonrandomized studies, are being increasingly recognized and include resolution of comorbidities such as diabetes, hypertension, and dyslipidemia. For extreme obesity, surgery is now the preferred and currently only effective treatment modality. Acute morbidity and mortality of surgical approaches have been dramatically reduced enabling widespread use of these procedures.[1]

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CHAPTER-6
ACUTE EMERGENCIES IN TYPE 2 DIABETES

Hypoglycemia:

- It is a common and potentially serious condition which usually occurs as a complication of treatment of diabetes mellitus. Hypoglycemia is defined as blood glucose level less than 70 mg/dl resulting from an imbalance between glucose supply, glucose utilization, and current insulin levels. The associated symptoms are due to neuroglycopenia. Recognizing hypoglycemia is important so that steps can be taken to prevent a medical emergency. When severe, seizures and loss of consciousness may occur.
- Hypoglycemia can be classified into mild, moderate and severe according to the severity.
- Mild hypoglycemia presents with symptoms like trembling, palpitation, sweating, anxiety, hunger and nausea. The individual is able to self-treat.
- Moderate hypoglycemia presents with neuroglycopenic symptoms like confusion, weakness, drowsiness, changes in the vision and difficulty in concentration in addition to symptoms of mild hypoglycemia. The individual is able to self-treat.
- Severe hypoglycemia requires assistance of another person. Unconsciousness may occur. Risk factors include prior history of hypoglycemia, strict glycemic control (HbA1c <6.0%), hypoglycemic unawareness, cognitive impairment and lower socioeconomic status.
- Management of hypoglycemia in the conscious patients is by giving 3 teaspoons of sugar or honey dissolved in 250ml of water. Blood glucose should be retested in 15 min. If it is still less than 70 mg/dl repeat oral ingestion of carbohydrate.
- The person should have usual meal or snack containing carbohydrate and protein that is due at that time to prevent repeated hypoglycemia. If meal time is more than an hour away, a snack containing 15 g of carbohydrate such as sandwich, biscuits or half chapatti along with portion of protein should be taken.
- Severe episode in an unconscious patient is treated by giving 20-50 ml of 50% dextrose water intravenously in 1-3 minutes.

Hypoglycemic unawareness:

- Sometimes people with diabetes treated with insulin or insulin secretagogues lose their ability to identify hypoglycemia, a condition known as hypoglycemic unawareness.This is due to repeated hypoglycemic episodes that reprogram trigger center for release of stress hormones at even lower blood glucose level. Recurrent hypoglycemia can reduce the hormonal and symptomatic responses to subsequent hypoglycemia, and, over time, after exposure to multiple episodes, patients can lose the ability to recognize hypoglycemia. Hypoglycemic unawareness can be managed by keeping the blood glucose above the desired range for few weeks to avoid hypoglycemic events. Frequent monitoring is advised in this condition and targets for glycemic control might need to be redefined.
- People with T2DM taking medicines which can potentially cause hypoglycemia should have proper education on prevention, recognition and management of hypoglycemia.

Hyperosmolar Hyperglycemic State (HHS):

- HHS is associated with significant morbidity and higher mortality than DKA and must be diagnosed promptly and managed intensively.[2,3]

- The clinical presentation is dominated by profound dehydration, without ketosis or significant acidosis. Plasma glucose level usually exceeds 600 mg/dl. If HHS continues, severe dehydration will lead to seizures, coma and eventually death. HHS may take days or even weeks to develop. The warning signs of HHS are dry, parched mouth, extreme thirst (although this may gradually disappear), warm, dry skin that does not sweat, high fever, sleepiness or confusion, loss of vision, hallucinations and absence of significant ketosis.

Diagnostic Criteria:

- Plasma glucose level of 600 mg/dl or greater
- Effective serum osmolality of 320 mOsm/kg or greater
- Profound dehydration, up to an average of 9L
- Alteration in consciousness

Management of HHS:

The goals of treatment are to treat the underlying cause and to gradually normalize the osmolality with replacement of fluid and electrolyte losses along with the correction of blood glucose. Other goals include prevention of thrombosis, cerebral edema, foot ulceration and bed sores.

Management at Primary Care

Urgently refer to secondary/ tertiary care. Meanwhile, the infusion of fluid with normal saline should be continued until hospitalization. Ten units of insulin should be administered immediately.

Management at Secondary Care

If secondary care provides in-patient facility, manage as tertiary care level, otherwise refer to tertiary care after maintaining intravenous line with 0.9% normal saline. Maintain intravenous infusion with normal strength saline until dehydration is corrected and urinary out flow is adequate. Fluid losses in HHS are estimated to be between 100-220 ml/kg.[2] The rate of rehydration will be determined by assessing the combination of initial severity and any pre-existing co-morbidities. Caution is needed, particularly in the elderly, as too rapid rehydration may precipitate heart failure.[2]

Management at Tertiary Care

- Measure or calculate osmolality (2Na+ + glucose + urea) frequently to monitor the response to treatment.
- Use intravenous (IV) 0.9% sodium chloride solution as the principle fluid to restore circulating volume and reverse dehydration. Only switch to 0.45% sodium chloride solution if the osmolality is not declining despite adequate positive fluid balance. An initial rise in sodium is expected and is not itself an indication for hypotonic fluids. The rate of fall of plasma sodium should not exceed 10mmol/L in 24 hours.
- The fall in blood glucose should be no more than 80mg/dl/hr. Low dose iv insulin (0.05 units/kg/hr.) should only be commenced once the blood glucose is no longer falling with IV fluids alone or immediately if there is significant ketonemia (3 α-hydroxy butyrate greater than 1 mmol/L or urine ketones greater than 2+).
- Intravenous fluid replacement aims to achieve a positive balance of 3-6 liters by 12 hours and the remaining replacement of estimated fluid losses within next 12 hours though complete normalization of biochemistry may take up to 72 hours.

- The patient should be encouraged to drink as soon as it is safe to do so and an accurate fluid balance chart should be maintained until I.V fluids are no longer required.
- Assessment for complications of treatment e.g. fluid overload, cerebral edema or central pontine myelinolysis (as indicated by a deteriorating conscious level) must be done frequently (every 1-2 hours).
- Underlying precipitants must be identified and treated.
- Prophylactic anticoagulation is required in most patients.
- All patients should be assumed to be at high risk of foot ulceration if obtunded or uncooperative, the heels should be appropriately protected and daily foot checks should be done

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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 mm Hg should have blood pressure confirmed on a subsequent day.
- 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)

- Systolic blood pressure (SBP) target should be <140 mmHg and diastolic blood pressure should be <90 mmHg in all people with diabetes and hypertension. There is limited evidence for the benefits of further lowering systolic blood pressure or diastolic blood pressure targets.
- If complications are present (additional risk factors and small vessel disease, particularly albuminuria), a tighter target may be appropriate.
- People above the age of 80 years may find it difficult to achieve a blood pressure below 145/85 mmHg because of presence of stiff vessels (IDF).

Therapeutic Management Strategies

- Patients with confirmed blood pressure readings of >140/90mmHg should be promptly initiated pharmacological therapy, in addition to life style modifications. Therapy must be titrated to achieve the desired goals.
- Lifestyle modifications consists of reducing excess body weight, increasing consumption of fruits and vegetables (4-5 servings per day), consuming low-fat dairy products (2-3 servings per day) and increasing activity levels
- Sodium intake is restricted; the restriction should be the same for people with and without diabetes. The simplest strategy is not to add table salt to meals.[5]
- For patients with diabetes and hypertension, ACE inhibitor/ARBs should be considered as initial therapy.[2,3]
- If target blood pressure level is not achieved after 2-3 months, addition of either a calcium channel blocker or

  βblocker or thiazide diuretic may be considered.
- Initial combination therapy may be needed when SBP is >20 mmHg and/or DBP is >10 mmHg above target, but this may vary with ethnicity and age.
- Achievement of target blood pressure level is critical. Multiple-drug therapy (including a thiazide diuretic and ACE inhibitor/ARB, at maximal doses) is generally required to achieve blood pressure targets.
- If ACE inhibitors, ARBs, or diuretics are used, serum creatinine and serum potassium levels should be monitored at day 10, then at 6 weeks and after that at every six to twelve months if it does not exceed more than 30% from its baseline.
- 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.[6]
- If blood pressure remains uncontrolled despite good compliance to optimal doses of at least three antihypertensive

agents of different class, one of which should be a diuretic, an evaluation for secondary hypertension should be considered.

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CHAPTER-8
DIABETES AND DYSLIPIDEMIA

- Dyslipidemia 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.[24]
- Dyslipidemia is 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).
- Obtain lipid profile at presentation, then at 4-12 weeks after initiation of statin therapy and then annually afterwards for intensification and to monitor the response of management. If lipid profile cannot be obtained at presentation, low dose statin is recommended for both primary and secondary prevention. This approach provides an opportunity for reducing rates of premature cardiovascular events.
- Lifestyle modifications specially targeting weight reduction in overweight or obese people and modification of diet is the mainstay of management of dyslipidemia.
- All patients with type 2 diabetes over the age of 40 years or below if they have an additional cardiovascular risk factor should receive statin therapy selected and up-titrated to reach an LDL cholesterol target <70 mg/dL (1.8 mmol/L), despite any level of baseline LDL, unless a very clear risk is identified to withheld the therapy.[1]
- All people with T2D and without established CVD who are ≥40 years old and have LDL cholesterol >100 mg/dL [2.6] mmol/L), should start treatment with a statin (primary prevention).
- Statin is the preferred medication. 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.
- Target LDL cholesterol to be lowered by 50 percent of the baseline or less than 100mg/dl. In patients with atherosclerotic cardiovascular disease risk factors LDL cholesterol target <70 mg/dl is advisable.[2,3]
- If triglycerides are high, more than 150mg/dl but less than 500mg/dl, strict lifestyle modifications, glycemic control and statins are recommended.
- If triglycerides are >500 to 1000 mg/dL (5.7-11.4 mmol/L) despite lifestyle changes and improved glycemic control should start a fibrate to prevent acute pancreatitis.[2,3]
- When a health care provider considers that the patient needs statin therapy, it should be maintained lifelong.

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CHAPTER-9
DIABETIC FOOT & PERIPHERAL ARTERY DISEASE

Diabetic foot lesions are responsible for more hospitalizations 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, paresthesias, rest pain, intermittent claudication etc.

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 color or shape of feet
- Loss of hair on the toes, feet, and lower legs
- Thickening and color 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 centers, Neurothesiometer can be used to assess vibration perception threshold (VPT).

◆ Assessment of vascular insufficiency:

- Screen for vascular insufficiency by palpating the foot pulses and/ or measuring the SBP to calculate the ankle/brachial index.

- If symptoms of peripheral disease are present and/or pedal pulses are absent 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 centers for further evaluation of PAD by color duplex ultrasound followed by CT angiography, MR angiography or standard X-ray angiography, if required.
- All patients with diabetes and an ischemic 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.

University of Texas Diabetic Foot Ulcer Classification System.[3,4]

Stage	Grade			
	0	I	II	III
A (no infection or ischemia)	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or Capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and	Infection and	Infection and	Infection and
	ischemia	Ischemia	Ischemia	ischemia

Management of Diabetic Foot ulcer:

Management Depends on the Type of Ulcer.

1. 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-ischemic (more frequent on the tips of the toes or the lateral borders of the foot) or ischemic by history and clinical examination.
2. Grading and staging of ulcer can be done using University of Texas classification (UT classification).
3. 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 ischemia.[4]

4. 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.
5. Daily saline or similar dressings to provide a moist wound environment.
6. Antibiotic therapy if osteomyelitis or cellulitis is present.
7. Offloading the wound by using appropriate therapeutic footwear.
8. Evaluation and correction of peripheral arterial insufficiency.
9. Deep ulcers requiring abscess drainage, involving bone or if an ulcer is identified as purely ischemic, refer to tertiary care center 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.

Table-1: Risk Classification system and preventative screening frequency.[3]

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 OF DIABETES

Microvascular complications of diabetes include Neuropathy, Nephropathy and Retinopathy.

Neuropathy:

Peripheral Diabetic Neuropathy (PDN):

- Diabetic neuropathies are the most common complications of diabetes affecting up to 50% of older people
- Screen every patient with T2DM for peripheral diabetic neuropathy (PDN) (as 50% patients are asymptomatic)
- All people with Type 2 Diabetes require assessment at the time of diagnosis and Type 1 Diabetics, require assessment five years after the diagnosis.
- Even symptomatic pre-diabetics should be screened at the time of diagnosis.
- Assessment should include careful history and examination should be based upon type of nerve fiber functions:

  1. Temperature and pinprick (small fiber functions)

  2. Vibration sensed by using tuning fork of 128 Hz. 10gm Monofilament testing, proprioception and ankle jerk (large fiber functions)
- Frequency of follow up assessment depends on presence of neuropathy and/or loss of protective sensations.
- The most common form of diabetic neuropathy is distal symmetric polyneuropathy usually occurring in stocking and glove pattern due to an axonal neuropathic process.
- Sensory involvement is bilateral, symmetric and usually results in decrease perception of vibration, pain and temperature.
- 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.
- The assessment of peripheral neuropathy includes testing with 10gms monofilament and any of the additional tests for pin prick, vibration or temperature sense.
- The tight glycemic control in Type 2 Diabetes has modest effect on risk of developing DPN1
- Treatment of PDN is usually unsatisfactory despite the availability of many drug classes
- Pregabalin, duloxetine, amitriptyline, gabapentin valproate and opioids like morphine, tramadol can all be used for Rx of painful PDN.
- Offer, amitriptyline, nortriptyline, duloxetine, gabapentin or pregabalin as initial treatment. Word of Caution regarding use of TCA in cardiac patients, may cause myocardial ischemia and arrhythmia.
- If initial treatment fails to improve symptoms or is not tolerated, offer second or third drug
- 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.

Diabetic Autonomic Neuropathy

1. Assessment and management of autonomic neuropathy may improve quality of life. It may present clinically with gastroparesis, diarrhea, constipation, fecal incontinence, increased or decreased sweating, orthostatic hypotension (a fall in systolic or diastolic blood pressure by 20 mmHg or 10 mmHg, respectively, upon standing without an appropriate increase in heart rate), resting tachycardia (>100 beats per min), neurogenic bladder and erectile dysfunction. (ED).
2. The risk of autonomic neuropathy can be reduced by lifestyle modifications, better glycemic control and cardiovascular risk modifications.
3. Assessment should include decreased heart variability with deep breathing by taking an ECG during 1 to 2 minutes of deep breathing.
4. Consider possibility of autonomic neuropathy in Patients with hypoglycemia unawareness.
5. Consider possibility of autonomic neuropathy affecting gut in diabetic patients with unexplained diarrhea particularly at night. Offer a trial of prokinetic drugs (metoclopramide, domperidone, erythromycin) for shorter duration in patients with suspected gastro paresis.
6. ED can result from neurologic, vascular, psychological causes or a combination of all of them.
7. Management of these complaints is symptomatic along with good glycemic control.

When to refer to neurologist?

- Atypical Clinical Features (Motor > sensory neuropathy)
- Different etiology is suspected
- Asymmetrical Presentation

Nephropathy

Diabetic nephropathy is the leading cause of end stage renal failure. It affects approximately 20-40% of diabetic patients.[1,2] All people with type 2 diabetes should be screened annually for presence of microalbuminuria.[3]

- Uncontrolled diabetes or hypertension, fever, infection, recent exercise or congestive cardiac failure may result in proteinuria without kidney disease.[4,5] Two readings three months apart should be taken before making a diagnosis of nephropathy.
- If proteinuria is present (≥ 30 mg of albumin/gram of creatinine per day) in two readings a low dose ACE inhibitor or ARB may be started even in normotensive people after taking baseline serum creatinine and potassium.[4]

An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in patients with diabetes who have normal blood pressure, normal urinary albumin to-creatinine ratio and normal estimated glomerular filtration rat.[5]

For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist which has shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both.[5]

- In non-pregnant patients with diabetes and hypertension the first line anti hypertensives are ACEI or ARBs. Combination of these drugs with each other should be avoided due to increased incidence of hyperkalemia.[6]
- 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.[7]

- Good metabolic control is essential to delay the progression of nephropathy.
- Dietary proteins should be restricted to 0.8mg/kg/day if macroalbuminuria is present.[5]
- If urinary albumin excretion is more than 300 mg/dl refer the patient to secondary care.
- Consider referral to tertiary care if kidney disease is rapidly progressive or in absence of retinopathy to evaluate for other causes of renal disease. Referral is also considered if anemia, resistant hypertension, electrolyte imbalance, any bone disease or secondary hyperparathyroidism is present.[4]

Retinopathy

- All people with type 2 diabetes should have detailed history regarding any existing eye problem. Refer for dilated eye examination by an ophthalmologist at diagnosis or first visit to the clinic.
- If no sign of retinopathy is present repeat examination annually. If retinopathy is present, frequency of examination should be suggested by ophthalmologist.
- Urgent referral is required in case of rapidly deteriorating vision, severe pain or any other eye emergency.
- Good metabolic control is mainstay of prevention or slow progression of retinopathy.

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