Indian Guidance on Cardiovascular and Renal Comorbidity Management in Type-2 Diabetes Mellitus

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Introduction

The global pandemic of diabetes is well-recognized, with the current prevalence rate approximating 8.5% of the adult population worldwide.[1] In India, the prevalence rate of 8.7% translates to >6.9 crore adult patients with diabetes. As an undesirable phenomenon in Indian epidemiology, the major burden of diabetes including its complications and mortality, affects the productive years of life.[2]

Background: CVD and CKD as Complications of T2DM

Cardiovascular disease (CVD) develops at an accelerated rate in Type-2 diabetes mellitus (T2DM). Atherosclerotic CVD (ASCVD) is known to occur nearly 14.6 years earlier in the presence of T2DM. The risk of Heart-failure (HF) is increased by 2.5 to 5 fold in T2DM.[3] HF is the second commonest manifestation of diabetic cardiomyopathy, and may also present very early in the course of disease.[4] CVD accounts for 2 out of every 3 deaths in patients of T2DM.[3] In the Framingham Offspring Study, 70.4% of the patients with diabetes were found to harbor subclinical CVD.[5] Recently, heart failure and peripheral arterial disease were found to be the most common manifestations of CVD in patients with T2DM.[4]

Chronic kidney disease (CKD) remains an insufficiently addressed complication of T2DM, affecting nearly 2 of every 5 patients.[3] Co-existence of CKD and T2DM represents a subset of patients, who are at markedly increased risk of mortality.[6] Moreover, CKD and diabetes are important risk factors for CVD. Presence of CKD has been associated with nearly 1.5-fold greater risk of major vascular events, stroke, and CHD, and 2-fold increase in the risk of mortality.[7] There has been a paradigm shift in our understanding of CKD in T2DM, as sizable portion of patients do have reduced estimated glomerular filtration rate (eGFR), with little or no albuminuria. In a recent longitudinal cohort study, subnormal eGFR emerged as a strong predictor of major CV events in diabetic patients, despite normoalbuminuria.[8] Both albuminuria and eGFR are now well-recognized independent predictors for CVD.

In patients of T2DM, multiple risk-factors often coexist, which may influence diverse pathophysiological processes. Hence, the scope of coexisting CVD or CKD in T2DM, maybe encompass progressive vascular complication(s) of uncontrolled glycemia (diabetic kidney disease or diabetic cardiomyopathy), influence of coexisting risk-factors like hypertension or dyslipidemia, and even the iatrogenic complications related to the use of medications.

The Indian Scenario: Is it Different?

The Asian-Indian Phenotype: While there would be similarities and differences across ethnicities, the epidemiology of T2DM in India may be expected to be worse, considering the Asian-Indian phenotype, and presence of other modifiable / non-modifiable risk-factors. Asian-Indian phenotype, distinguished by greater degree of central obesity (larger waist circumference and waist-to-hip ratio), hyperinsulinemia and insulin resistance, atherogenic dyslipidemia (low levels of HDL-Cholesterol and high level of triglycerides) predispose Indians to T2DM and premature CVD.[9,10]

CVD and CKD in Indian Patients of T2DM: Indian epidemiological evidence, despite its limitations in being accurately nationally representative, or in using varied definitions for the comorbidities, collectively reflects a significant existing burden of vascular complications in diabetes. The baseline data available from the A1chieve study found a high prevalence of diabetic microvascular as well as macrovascular complications. Neuropathy (24.6%) was the most common complication, followed by cardiovascular (23.6%), renal (21.1%) and ocular (16.6%) complications.[11] An outpatient study (SITE), demonstrated nearly 2-fold increased risk of myocardial infarction (MI), stroke, or ischemic heart disease (IHD), in the presence of diabetes.[12] Community-based evidence from an Indian study (CUPS), suggests a 2.35-fold higher risk of coronary artery disease (CAD) in presence of diabetes, as compared to normal glucose tolerance.[13] Similarly, a community-based screening for CKD in the adult Indian population (SEEK), suggested

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Table 1: Percentage of patients in I CARE survey with risk factors for CVD/ CKD

Symptoms/ Signs		Laboratory Investigations	
Any risk factor	95%	Uncontrolled HbA1c	71.3 %
Long-standing T2D (≥10y)	39.2%	Abnormal lipid profile	63.7%
H/o hypertension	68.8%	eGFR < 90ml/ min/1.73m^2	53.0%
H/o dyslipidemia	71.8%		
H/o smoking (current)	16.0%		
Family h/o CVD	33.6%		
Central obesity	62.1%		
Presence of retinopathy	21.9%		
Abnormal pulse	10.1%		
Abnormal monofilament	30.9%		

nearly 2-fold increased risk of CKD, in the presence of diabetes.[14]

Silent organ damage is of considerable relevance to T2DM. In the CUPS study, while documented MI was observed in only 3.4% of the patients of diabetes, the prevalence of subclinical atherosclerosis was significantly higher. As a corollary, overall CAD was observed at a >6-fold higher rate, in 21.4% of the patients of diabetes.[13] Apart from subclinical ASCVD, chronic kidney disease (CKD) generally pursues a silent progression to renal failure, or to a cardiovascular event. Strikingly, in the 'Joint Asia Diabetes Evaluation' (JADE) registry, which assessed the diabetes-care standards across seven Asian countries, the Indian patients ranked highest in the prevalence of CKD, and second highest in the prevalence of albuminuria.[15]

The development of vascular complications begins early in T2DM. An Indian cross-sectional study in newly-diagnosed patients of T2DM (CINDI), demonstrated high prevalence of microvascular complications, and risk-factors for CVD, early in the course of diabetes. Amongst the newly-diagnosed patients of T2DM, 13.15% had neuropathy, 6.1% had retinopathy and 1.06% had nephropathy. Risk-factors for CVD, such as hypertension, obesity, and dyslipidemia were observed in 23.3%, 26%, and 27% of newly-diagnosed patients, respectively.[16] The prevalence of microalbuminuria and macroproteinuria were found to be 24.7%, and 6.2% in Indian patients with duration of diabetes less than 1 year.[17]

Rule of Two Thirds: Based on the comprehensive Indian evidence, the rule of two thirds serves as an underlying principle in the Indian epidemiology of diabetes.[18] The rule suggests that nearly a third of the patients are being actually diagnosed with diabetes, and two-third of the patients would not have HbA1c assessment done even once annually. Two-third of the patients, are young in age, and an equivalent proportion would not have a family history of T2DM. Further, only one-third of the patients adhere to recommendations of exercise and self-monitoring, whereas two-third adheres to dietary and therapeutic recommendations. Overall, only a third of the patients are appropriately controlled for HbA1c. This evidence does suggest a good scope, for enhancement in the existing diabetes care practices, across India.

Congruence of Situation, Knowledge, Attitude, and Practice: A nationwide survey to assess the existing situation, knowledge, attitude, and practices related to the management of cardiovascular and renal comorbidities in T2DM, suggested some key observations. This cross-sectional survey represented nearly 300 Indian physicians with a sound clinical expertise in diabetes care, and 5 of their consecutive patients of T2DM. While most physicians believed that 20-40% of their patients had CVD, the patient-records suggested 26.7% of patients to be known-cases of CVD; importantly, the point-prevalence of CVD rose to 37.3%, when the abnormalities in ECG / 2D-Echo / Treadmill test findings were also considered. Moreover, in patients without a known history of CVD, 95% of the patients had a predisposing risk for CVD or CKD, as described in Table 1.

The observations regarding CKD had, in fact, been more conspicuous. While most physicians agreed that 20-40% of their patients of T2D had CKD, the point-prevalence of CKD in patients with available assessments, was actually 64.7%. Nearly 43% of the patients of T2D, had 'Early CKD', identified by the presence of either moderate-grade albuminuria (micro-albuminuria; UACR 30-300 mg/g creatinine), or eGFR level being in the range of 89-60 mL/min/1.73m^2. According to the KDIGO definition of CKD, moderate-grade albuminuria, as well as eGFR <90 mL/min/1.73m^2, qualify as the criteria for diagnosing CKD. Moreover, considering the phenomenon of hyperfiltration in diabetic kidney disease, an eGFR of <90 mL/min/1.73m^2 could suggest a considerable decline in renal function.[20] 'Overt CKD' was observed in 21.7% of the patients of T2DM, identified by the presence of either severe-grade albuminuria (macro-albuminuria; UACR >300 mg/g creatinine), or by eGFR level being <60 mL/min/1.73m^2. This data has limitations, since the MDRD equation has not been validated for the Indian population, and also since the mean eGFR level is relatively lower in the healthy Indian adults, as compared to the western reference. A large study in about a thousand Indian healthy adults, suggested the mean eGFR to be 87.4 mL/min/1.73m^2; 97% of the values were in the range of 77.4 to 97.1 mL/min/1.73m^2.[20] Considering this reference range of eGFR, 53.1% of the survey population had CKD, identifiable by a lower than normal eGFR, or positive albuminuria.

To summarize, nearly a third of the patients did demonstrate existence of CVD, and over half of the patients did demonstrate existence of CKD, in this assessment of Indian patients of T2DM, in an outpatient clinical setting.

More importantly, most of the physicians did agree that regular assessment of albuminuria, as well as eGFR, should be a routine consideration in the patients of T2DM. The patient-records suggested that >90% of the patients had been assessed for albuminuria and serum creatinine; however, the information on eGFR calculation was available for only 55% of these patients. Further, most physicians did realize the importance of regular renal function assessment, but found eGFR-based therapeutic approach to be a practical challenge. This observation clearly highlights the discordance in the existing knowledge, versus clinical practice.

Collectively, the available evidence indicates a clear need for educational and translational efforts, towards optimizing the management of cardiovascular and renal comorbidities, in the Indian patients of T2DM.

Objective and Scope

This guidance statement is intended to serve as a reference source for the

Table 2: Levels of prevention

Levels of prevention	Primordial	Primary	Secondary	Tertiary	Quaternary
Target population	General Population	Susceptible	Asymptomatic	Symptomatic	Symptomatic
Goal	Prevent Risk Factors	Prevent Disease Development	Early Detection and Treatment	Prevent Complications	Prevent Over-Medicalization and Unnecessary Treatment

Indian physicians, having an interest in the management of T2DM and its complications, including CVD and CKD.

Although this statement summarizes the pertinent scientific and clinical aspects, detailed approach of each strategy is beyond the scope, and the reader is referred to the specific literature for additional information. The definitive management of CVD and CKD, including recipients of dialysis or transplantation, is also not in the scope of this statement.

In this statement, emphasis has been given to the preventive, diagnostic and treatment aspects of T2DM, with coexisting CVD and / or CKD in adult patients. Specific considerations related to children, pregnant women, and other special patient-groups, may not be expected from this statement. While the general therapeutic goals and considerations have been described, it is essential to realize the importance of individualized patient-centric management approach, for optimal delivery of healthcare services.

A steering committee of experts has guided the development of this statement, through detailed academic contributions. A separate advisory board of experts has helped in further shaping this guidance statement, to its current form. Much emphasis has been laid to incorporate perspectives based on up-to-date scientific evidence; however, expert-group opinion has been given due emphasis, wherever appropriate.

Outline

The guidance is drafted to cover four diverse aspects, related to the management of cardiovascular and renal comorbidities in T2DM.

a. Prevention Paradigm
b. Management of CVD and CKD in T2DM
   i. Diagnostic approach
   ii. Therapeutic approach

Prevention Paradigm

Prevention Paradigm in Cardio-renal Continuum

Altering the natural course of disease, through effective interventions targeted at possible opportunities, has been increasingly realized. In 1991, Dr. Dzau and colleagues originally proposed the clinical approaches to 'Prevent', 'Regress', or 'Retard' the development of cardiovascular disease and chronic renal disease, along its evolution.[21]

This 'Cardio-renal continuum', represents an evolutionary landscape of CVD or CKD, divided in 3 clinically pertinent stages.

- **Stage 1**: Clinical identification of only the risk-factors.

  Clinical Approach: 'Prevent' organ-damage.
- **Stage 2**: Asymptomatic target-organ damage (identified by clinical or laboratory signs, like albuminuria, decline in eGFR, left-ventricular hypertrophy, etc.).

  Clinical Approach: 'Regress' organ-damage.
- **Stage 3**: Symptomatic target-organ damage (established CVD / CKD).

  Clinical Approach: 'Retard' organ-damage.

While the understanding of CVD and CKD has evolved ever since, the cardio-renal continuum still assumes a benchmark clinical approach to manage chronic diseases.

The cardio-renal continuum is analogous to the 3 levels of prevention, originally coined by Leavell and Clark, which included:

- **Primary Prevention** (Prevention): Measures to avoid the development of disease
- **Secondary Prevention** (Treatment): Measures for early detection and treatment of disease
- **Tertiary Prevention** (Rehabilitation): Measures to reduce harm from symptomatic disease

Two new concepts had been further additionally introduced in preventive medicine, including:

- **Primordial prevention**: Measures to prevent development of risk-factors for disease
- **Quaternary prevention**: Measures to avoid over-medicalization and unnecessary interventions

While the broader aspect of primordial prevention remains out of scope for this guidance, the vital importance of measures to avoid the development of cardiovascular risk factors, including hypertension, dyslipidemia, obesity and diabetes, cannot be emphasized enough.

For a patient of T2DM, these aspects of prevention of CVD, and CKD, need effective translation in clinical practice, through meticulous healthcare delivery.

Management of CVD and CKD in T2DM

I. Diagnostic Approach

A. Holistic Assessment of CV Risk in T2DM: Risk assessment for CVD and CKD, facilitates individualization of clinical approach, in the management of patients with T2DM. The aspect of T2DM being labelled as a 'CAD equivalent', has been debatable; the acceptable classification would be based on the CV risk categories of the individual patients. The approach for ASCVD risk management in Indian patients, recommends that presence of T2DM itself should be considered in "High CV-risk" category.[22] In presence of target-organ damage, or ≥2 additional major CV risk-factors, the patient of T2DM should be considered in "Very high CV-risk" category.

The major CV risk-factors include:

1. Age ≥45 yrs. in males or ≥55 yrs. in females
2. Current smoking or tobacco use
3. Family history of early ASCVD (<55yrs of age in male first-degree relative, or <65yrs of age in female first-degree relative)
4. High BP or receiving BP medication
5. Low HDL-C level

a. Risk-factors and Predictors for CVD: The traditional risk factors for CVD can be classified as modifiable and non-modifiable, wherein modifiable risk factors if controlled and treated can lead to reduction in CVD risk. For Indian population, the risk-factors for CVD may be classified as:

- **Non-modifiable risk factors**: Age, Family history, Ethnicity.
- **Modifiable risk-factors** include two major aspects:
- Cardio-metabolic risk-factors (hypertension, dyslipidemia, diabetes mellitus, obesity)
- Lifestyle risk factors (smoking, physical inactivity, nutrition)

b. Other Predictors for CVD, Relevant to Clinical Practice:

- **Cardiovascular risk-scores** have been developed for the general population as well for people with diabetes based on the identification of risk-factors and predictors in clinical trials.[23-25] Though these risk-scores have good application in the population in which they were developed, validation is warranted in other populations. The Joint British Societies 3rd Iteration (JBS3) risk-calculator[26] and Q-RISK score[27] appear to provide the most accurate CV risk estimates for the Indian patients.
- **Albuminuria** is a predictor for future cardiovascular events (MI, stroke or CV death), CHF, and all-cause mortality in patients of T2DM, even after adjusting for other risk factors.[28]
- **Electrocardiogram (ECG) and Treadmill test:** This is a simple noninvasive method, which can detect evidence of prior MI or ischemia.
- **Other cardiovascular biomarkers** that promote formation and progression of atherosclerosis have high potential for risk stratification.
- Lp(a) is an important marker for ASCVD risk in Indians, particularly in those with family history of premature CAD. Lp(a) value of >20 mg/dL indicates increased ASCVD risk in Indian patients.[22]
- Plasma N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) is also a strong predictor of cardiovascular mortality, independent of albuminuria and conventional risk factors.
- Ankle- brachial index (ABI), Carotid intima-media thickness (CIMT), Arterial stiffness by pulse wave, and Cardiac autonomic neuropathy by standard test, are useful cardiovascular markers, which add predictive value to the usual risk estimate.
- Coronary Artery Calcium (CAC) screening offers the most sensitive tool for asymptomatic individuals with DM. Further, CAC imaging is currently a Class IIa recommendation by ACC/AHA guidelines for screening in such a population.[29] CAC scoring can be a good screening tool for identifying subjects with occult CAD in low and intermediate risk populations.
- Highly-sensitive C Reactive Protein (hsCRP) is a simple assessment to detect vascular complications. Its routine use in Indians is not recommended due to issues related to standardization of assays and the high prevalence of infectious diseases in our country.
- Hyperhomocystinemia maybe commonly observed in Indians due to cobalamine deficiency. However, the routine assessment of serum homocysteine levels, for CVD risk assessment, is not recommended.

c. Screening for CAD and HF in T2DM

- **Screening of CAD in T2DM**: Screening for CAD is not recommended in all T2D patients. Screening for CAD is recommended in presence of atypical cardiac symptoms; signs or symptoms of associated vascular disease, including carotid bruits, stroke, TIA, claudication or PAD; and electrocardiogram abnormalities.
- **Screening for HF in T2DM**: Screening for HF should be considered for all T2D patients above 50 years of age. A simple screening is possible on the basis of routine clinical assessment (history, symptoms and clinical signs), as summarized in Table 2.[31] Although the tool has been validated for Caucasian patients of ≥60 years of age, HF is known to occur at a younger age, in South Asian patients.[31]

d. Monitoring Patients of T2DM with Established CVD: In patients with T2DM and established CVD, despite stable clinical variables, regular assessment of biomarkers like hsTnT, NT-proBNP, and hsCRP should be considered to identify ongoing vascular damage. Regular follow-up for CV assessments, as suggested by the appropriate specialty experts, should be re-iterated.

B. Holistic Assessment of CKD Risk in T2DM: As renal damage may remain subclinical for a few years before the first signs of kidney disease become evident (microalbuminuria or decline in GFR), early detection of CKD is often missed. For optimal early detection of CKD in T2DM, due consideration must be given to clinical predictors, as well as laboratory investigations. Regular follow-up assessment is a key component of effective management of CKD in T2DM.

a. Clinical predictors of CKD: Since CKD may remain subclinical for a long duration in T2DM, the clinical predictors of CKD risk should be assessed for each patient, at the time of **initial diagnosis** of T2DM, as well as on a **regular basis** subsequently. These include:

- Presence of hypertension
- Presence of dyslipidemia
- H/o Smoking
- Poor glycemic control
- Family history of DKD
- Presence of other vascular complications

Each of these risk-factors independently predisposes to the development of CKD.

b. Laboratory investigations:

Earliest detectable signs of CKD include:

- **Albuminuria** (moderate-grade or micro-albuminuria / severe-grade or macro-albuminuria)
- **eGFR** level
- **Serum creatinine**, by itself, may be misleading as an accurate indicator of renal function

Screening should commence at

the time of **initial diagnosis** of T2DM, and repeated **at-least once every year** thereafter. This should include urinary albumin-creatinine ratio (UACR) in a spot-urine sample, serum creatinine level, and importantly, the eGFR level. More frequent assessment of eGFR is required (at 3-6 monthly intervals), in patients with eGFR levels of <60mL/min/1.73m^2.

An elevated UACR should be confirmed in the absence of urinary tract infection, with 2 additional first-void specimens collected during the next 3 to 6 months.

eGFR level can be estimated by using the CKD-EPI equation, or the MDRD equation. CKD-EPI equation is generally more accurate in early CKD, whereas MDRD equation is more accurate when the eGFR is <60mL/min/1.73m^2. Although the validity of any eGFR equation has not been confirmed in the Indian population, CKD-EPI-Pakistan is considered as the closest estimate. We need to validate the eGFR in India as well, to avoid over diagnosis of CKD.

The assessment of eGFR levels has significant diagnostic and therapeutic implications in the management of T2DM.

Increased levels of **alkaline phosphatase** have been associated with renal hyperfiltration, as well as albuminuria.[32] This may be considered as an early predictor of CKD. **Serum cystatin C** may be a more accurate marker; however, as per the KDIGO working group recommendation for DKD, testing for serum cystatin C is unlikely to have a significant role in clinical practice.[33] The utility of other biomarkers of renal damage, like **serum alpha-2-HS-glycoprotein**, **alpha-1-antitrypsin**, or **alpha-1-acid glycoprotein**, in the clinical management of CKD, is currently in an evolutionary stage.

Guiding Principles: Holistic Assessment of CVD and CKD in T2DM

- Presence of T2DM alone qualifies as "High CV-risk" condition. Presence of ≥2 additional CV risk-factors, or target organ damage, qualifies as "Very high CV-risk" condition.
- Screening for CAD is recommended in patients of T2DM, with insufficient control of CV risk-factors, or with signs and symptoms of CVD (like angina, carotid bruits, transient ischemic attack, stroke, claudication, erectile dysfunction, or abnormal ECG findings).
- Routine clinical screening for HF is recommended for patients of T2DM, aged ≥50 years. For younger patients of T2DM, symptoms like increasing breathlessness, or identification of other vascular complications, should prompt the assessment for HF.
- Clinical predictors for CKD, based on the patient's history, should be assessed for every patient of T2DM at the time of diagnosis, and at subsequent visits as appropriate.
- Albuminuria, and eGFR, both have independent diagnostic and therapeutic implications. eGFR must be assessed, as mere Serum creatinine assessment may mislead interpretation.
- Albuminuria, Serum creatinine, and eGFR, must be assessed at the time of diagnosis of T2DM, and followed-up at-least once annually. A positive albuminuria finding should be confirmed by 2 additional assessments, each being at-least 1-3 months apart.

II. Therapeutic Approach

Therapeutic Goals and Considerations

a. Lifestyle Modification

- Weight management:

- Sustained loss of >5% body-weight is recommended in those who are overweight / obese. Sustained weight-loss of ≥7% is optimal.

- Diet regimen should be individualized based on the patient-preferences, to ensure the overall requirements for calorie-restriction.

- **Dietary management:** Characteristics of a healthy diet include the following:

- There has been growing evidence that high carbohydrate diet, which is generally seen in Indian scenario, may be linked to increased mortality. In a prospective cohort study, Prospective Urban Rural Epidemiology (PURE), high carbohydrate intake was associated with a higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality. Accordingly, we recommend moderation of total dietary carbohydrate, at the same time maintaining adequate calorie intake.

- Saturated fatty acids should provide <10% of total calorie intake. Trans-unsaturated fatty acids to be minimized to <1% of total calorie intake, derived from natural sources (processed foods should be avoided).

- 30 grams of nuts and 30-45 g of fiber are recommended per day.

- 2-3 servings of fruits, as well as vegetables are recommended per day (≥200 g).

- <5 g of salt is recommended per day.

- Consumption of fish is recommended 1-2 times per week.

- Consumption of alcoholic beverages should be limited to 2 glasses per day (20 g/d of alcohol) for men and 1 glass per day (10 g/d of alcohol) for women.

- Consumption of sugar-sweetened and alcoholic beverages must be discouraged.

- In patients of T2DM with CKD (stages 1-4), recommended daily protein intake should be 0.8 g/kg body weight. An increased intake of carbohydrates and/or fats may be required to maintain the caloric balance. Increasing intake of omega-3 and monounsaturated fats may be relevant.

- **Exercise:** For Indian adults, the following exercise regimen is recommended:

- Physical inactivity should be avoided as far as possible.

- For substantial health benefits, adults should do at-lease 150 minutes a week of moderate-intensity, or 75-minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 minutes, and preferably, it should be spread throughout the week.
- For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 minutes (5 hours) a week of moderate-intensity, or 150 minutes (2 hours 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount.
- Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week. However, time spent in muscle-strengthening activities does not count toward the aerobic activity guidelines.
- The exercise regimen should be customized to individual needs and capacities.
- Effort should be ensured to minimize the risk of hypoglycemic event during exercise.
- In patients with diabetic retinopathy, an ophthalmology consultation should be considered before initiating rigorous exercise.
- In patients with diabetic neuropathy, meticulous foot-care must be ensured on a regular basis. Weight-bearing activities may-be avoided in presence of foot-injury.
- In patients of diabetic autonomic neuropathy, initial cardiac workup is recommended, to minimize the risks associated with silent ischemia.
- Prolonged sitting should be interrupted at every 30 min interval. Sedentary lifestyle should be minimized.

• **Stress Management:** Stress management through indigenous techniques like yogasanas, pranayama (deep breathing) and meditation should be incorporated in daily life. They may help reduce stress and thus may improve lifestyle of patients.

• **Smoking and Alcoholism:**

- Efforts towards smoking cessation should be an integral part of diabetes care.
- Tobacco consumption and smoking must be completely avoided.
- Alcohol intake, even in moderation, should be avoided by Indians. This is because any benefit of moderate alcohol consumption, has not been evident in Indians.[22] For patients who drink, alcohol should not exceed 1 drink per day for women or up to 2 drinks per day for men.

b. Glycemia control

• Therapeutic goal for HbA1c:

- In patients of T2DM: <7% should be aimed as a general therapeutic target.
- In patients who are not frail and who do not have CVD, a target of <6.5% should be considered.
- In patients with a long duration of DM, the elderly, frail, or those with existing CVD, less stringent HbA1c targets should be considered.

• Therapeutic Considerations

- Metformin should be considered as the first line agent in most patients, unless contraindicated or not tolerated.
- Attempts should be made to achieve the therapeutic goal of HbA1c in patients, without increasing the risk of hypoglycemia, or excessive weight-gain. SGLT2-i agents and incretin-based therapies may benefit these clinical considerations.
- In patients with T2DM and established atherosclerotic cardiovascular disease, drugs which have demonstrated CV protection or benefit, like Empagliflozin, Liraglutide etc. should be considered to reduce cardiovascular and all-cause mortality, when added to standard care.
- The CV safety profile of antidiabetic agents is an important consideration in making therapeutic choices. Agents with known evidence of CV safety should be preferred over those having unknown or questionable CV safety.
- In patients with T2DM and HF:

▪ Glycemic control should be implemented gradually and moderately.

▪ Metformin is safe to use in patients with HF with reduced ejection fraction (HFrEF), and should be the first agent for patients with HF. Metformin is contraindicated in patients with severe renal or hepatic impairment, because of the risk of lactic acidosis.

▪ Insulin has a powerful sodium-retention property, and its use may result in fluid retention, leading to worsening of HF. However, it still remains the treatment of choice in acute decompensated states. Some sulphonylureas have also been associated with an increased risk of HF.

▪ Pioglitazone causes sodium and water retention, and worsens HF. Its use is not recommended in patients with HF. Saxagliptin has been associated with an increased risk of HF-related hospitalizations, and its use should be avoided in such patients.

▪ Empagliflozin has demonstrated reduction in hospitalization for HF and CV mortality, in patients of T2DM and established CVD. Canagliflozin, on the other hand, demonstrated a significant reduction in hospitalization for HF, but did not show a significant reduction in mortality. Use of these agents may be considered in such patients, who have a higher risk of HF. When an SGLT2-i agent is combined with a loop diuretic, the risk of volume-depletion increases. The dose of the diuretic should be adjusted accordingly.

▪ GLP-1 receptor agonists cause an increase in heart-rate. A recent trial of liraglutide in patients of HF, did not demonstrate any clinical benefit.

- In patients with T2DM and CKD:

▪ Maintenance of good glycemia control (HbA1c level <7%), reduces the risk of developing microalbuminuria, as well as macroalbuminuria. Good glycemia

control also slows the rate of decline of GFR.

- Appropriate dose-adjustments of antidiabetic agents should be made, based on the eGFR levels.
- When the eGFR levels fall to <60mL/min/1.73m^2, and/or the patient develops macroalbuminuria, the patient should be referred to a nephrologist for elaborate evaluation of CKD.
- Amongst the DPP4-i agents, linagliptin[35] and saxagliptin[36] have demonstrated some evidence of possible reno-protection, beyond glycemic control. In a meta-analysis of 13 Phase 2 & 3 clinical trials of linagliptin, a statistically significant reduction was observed in the composite renal endpoint comprising of new onset moderate albuminuria, new onset severe albuminuria, reduction in kidney function, halving of eGFR, acute renal failure and death[37]. This may suggest a possible renal protection. However, a confirmatory trial, CARMELINA is ongoing, which would serve as a confirmatory evidence for the same. Renal endpoints were also studied in SAVOR TIMI 53 trial[36] in a post-hoc analysis. There was no significant change in the confirmatory parameters for renal protection, like doubling of serum creatinine, initiation of dialysis, renal transplant or serum creatinine and death due to renal disease. There was evidence of albuminuria reduction with saxagliptin. However, albuminuria reduction does not correlate well with renal protection in long-term.
- SGLT 2 inhibitors have also demonstrated possible renoprotection in terms of reduced decline in eGFR, as well as reduction in new-onset macroalbuminuria, and regression of macroalbuminuria. However, SGLT2-i agents should not be used in patients with eGFR of <45mL/min/1.73m^2. Dapagliflozin and canagliflozin have been associated with acute kidney injury. SGLT2-i agents should not be used in volume-depleted patients, and hydration should be adequately maintained during SGLT2-i therapy. SGLT2-i agents may also increase the risk of urinary tract infections (UTIs), particularly in patients having an anatomical obstruction to the urinary tract, or those known to have recurrent UTIs. These agents should be used cautiously with the stronger diuretic agents.[38]

c. Hypertension management

- Blood-pressure should be monitored at every routine visit of the patient.
- Therapeutic Goals:
  - General recommendation in T2DM: Goals of <140mmHg for systolic BP, and <90mmHg for diastolic BP.
  - In patients with higher risk of CVD: Goals of <130mmHg for systolic BP, and <80mmHg for diastolic BP, if achievable without undue burden.
  - In patients with CVD, who are relatively younger and can tolerate lower BP: Goal of <120mmHg for systolic BP maybe considered, based on the patient's informed willingness, and/or in cases with increased predisposition to stroke.
  - In patients with CKD (stages 1-4): Goals of <130mmHg for systolic BP, and <80mmHg for diastolic BP.
  - Chronic hypertension in pregnancy: In known cases of mild chronic hypertension, goals of <160mmHg for systolic BP, and <100mmHg for diastolic BP are recommended. In patients with target organ damage, goals of <140mmHg for systolic BP, and <90mmHg for diastolic BP are recommended.
- Treatment considerations:
  - In patients with BP >120/80mmHg, lifestyle modification is recommended.
  - In patients with BP levels above therapeutic goals, approach aimed at rapidly achieving goal BP, and maintaining sustained control of BP, should be considered.
  - ACE-inhibitors, ARBs, thiazide-like diuretics, or dihydropyridine calcium channel blockers (CCBs) may be considered as the first-line therapy. In patients with CKD, ACE-i or ARBs should be the preferred agents. A combination of ACE-i and ARB is not recommended.
  - In patients being treated with ACE-i, ARB or a diuretic, eGFR, serum potassium and electrolyte levels should be monitored. Care must be observed when these agents are combined with SGLT2-inhibitor agents.
  - Diuretics may cause hypokalemia, which may result in QT-interval prolongation as an adverse-effect. These drugs should be avoided in patients with long QT syndrome, or in patients at higher risk of CVD, who are receiving other drugs that may prolong QT-interval, like teneligliptin.

d. Lipid management

- Lipid profile should be assessed at diagnosis or initial evaluation, and be repeated at every 5 years thereafter, or more frequently if indicated. After an abnormality is detected, lipid profile should be assessed annually.
- Therapeutic Goals and Considerations:
  - LDL-C is the primary therapeutic target for ASCVD risk management. Non HDL-C (Total cholesterol minus HDL-C), is particularly relevant in Indian patients, and is recommended as a co-primary therapeutic target, by the Lipid Association of India. Level of Non HDL-C should remain within 30mg/dL of the LDL-C level.
  - In patients of T2DM an LDL-C goal of <70mg/dL, and non HDL-C goal of <100mg/dL is recommended.
  - In patients of T2DM, with CVD or ≥2 additional major CV risk-factors (Very-high CV risk category), LDL-C goal of <50mg/dL, and non HDL-C goal of <80mg/dL is recommended. However, LDL-C goal may be relaxed to <70mg/dl, if high doses of statins are required which may not be well tolerated.
  - Statins remain the first-line therapy in all patients, except in patients with very high Triglyceride levels (>500mg/dL), or in patients undergoing hemodialysis who do not have a specific cardiovascular indication for treatment.
  - The choice of statin therapy depends primarily on the extent of LDL-C reduction targeted, rather than any individual agent. There is some evidence to suggest a benefit of atorvastatin over rosuvastatin,

particularly in patients of T2DM with CKD. Depending on the intended therapeutic goal, moderate or high intensity statin therapy may be required:

- Moderate-intensity statin therapy: Statin dose that is expected to reduce LDL-C by approximately 30 to <50%.
- High-intensity statin therapy: Statin dose that is expected to reduce LDL-C by ≥50% from baseline.

- Following achievement of LDL-C goal with lifestyle measures and statin therapy:

- Non HDL-C goal and Triglyceride levels should be observed. Recommended goal for Triglyceride level is <150mg/dL (preferably <100mg/dL).
- In case the Non HDL-C level or Triglyceride level remain high, intensification of lifestyle measures and statin therapy must be considered as the next step. A non-statin drug like fibrate or ezetimibe should be considered for addition only when these above measures fail to provide adequate control, or in cases of statin intolerance.
- In patients with very high Triglyceride levels of >500mg/dL, the first consideration is to avoid an event of pancreatitis. In such patients, non-statin drugs like fibrates, omega-3 fatty-acids should be initiated to ensure priority control of Triglyceride levels. This may be followed by statin therapy, to achieve the LDL-C and Non HDL-C goals.

- HDL-C level should be >40mg/dL in males, and >50mg/dL in females.

- For raising the low HDL-C level, vigorous lifestyle modification measures, and statin therapy, remain the mainstay of treatment.

e. Use of Antiplatelet agents

Primary prevention of CVD:

- Aspirin is generally not recommended for the primary prevention of CVD in T2DM.
- In patients of T2DM having ≥2 additional major CV risk-factors (Very high CV-risk category, but no target-organ damage), low-dose aspirin (75-162 mg/day) may be used for primary prevention of ASCVD, if these patients do not carry an increased bleeding tendency.

Secondary prevention of CVD:

- In patients with T2DM and established CVD, low-dose aspirin therapy (75-162mg/day) is recommended as a secondary prevention strategy.
- Clopidogrel (75 mg/day) may be considered as an alternative, in patients who are intolerant to aspirin.
- Dual antiplatelet therapy may be considered following an event of acute coronary syndrome.

Multifactorial Approach and Early Intervention

The alphabet strategy as advocated by Patel et al is a comprehensive diabetes care checklist consisting of a mixed approach including advice on lifestyle modification, blood pressure management, cholesterol management, diabetes control, eye examination, foot examination and use of guardian drugs such as aspirin, RAAS blockers and statins.[39, 40] The Steno-2 study randomized T2DM patients to conventional treatment against intensive treatment (with median disease duration of 5.5–6.0 years) with persistent microalbuminuria. The intensive treatment consisted of stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin. Patients had a mean HbA1c of 8.4%–8.8% and median disease duration of 5.5–6.0 years. During the first 3.8 years of follow-up, intensive versus conventional therapy reduced the risk of nephropathy (OR, 0.27 [95% CI 0.10, 0.75]; P=0.01), retinopathy (OR, 0.45 [95% CI 0.21, 0.95]; P=0.04), and autonomic neuropathy (OR, 0.31 [95% CI 0.12, 0.78]; P=0.01).[1] Reductions were maintained after a mean 7.8 years of additional follow-up (nephropathy HR, 0.39 [95% CI 0.17, 0.87]; P=0.003 and retinopathy HR, 0.42 [95% CI 0.21, 0.86]; P = 0.02). After 7.8 years, intensive therapy decreased the risk of the primary composite macrovascular endpoint (unadjusted HR 0.47 [95% CI 0.24, 0.74]; P = 0.008). After a mean follow-up of 17 years, the original intensive therapy group had an absolute RR of 2.8% for composite CV endpoints. The authors concluded that the use of statins and antihypertensive drugs may have had the largest effect on long-term CV risk. [41, 42, 43]

Combination treatment for blood pressure lowering and intensive glucose control lead to additional reductions in clinically relevant endpoints. Combination treatment reduced the risk of new or worsening nephropathy by 33% (95% CI 12-50%, P = 0.005), new onset of macroalbuminuria by 54% (35-68%, P < 0.0001), and new onset of microalbuminuria by 26% (17-34%) and risk of all-cause death by 18% (1-32%, P = 0.04).[44]

Thus multifactorial approach can reduce both CVD and all-cause mortality and also improve renal outcomes.

Guiding Principles: Holistic Management of T2DM

- Lifestyle modification, consisting of dietary management, weight control, exercise and abstinence from smoking and alcohol remains the mainstay for management of all T2D patients.
- An HbA1c value of <7% should be aimed as a general therapeutic target. However, the therapeutic HbA1c goal should be individualized based on the patient's general status, age and frailty.
- Attempts should be made to achieve the therapeutic goal of HbA1c in patients, without increasing the risk of hypoglycemia, or excessive weight-gain
- Agents with known evidence of CV safety should be preferred. In patients with T2DM and established cardiovascular disease, drugs which have demonstrated CV protection or benefit may be considered in addition to the standard care.
- Appropriate dose-adjustments of antidiabetic agents should be made, based on eGFR level.

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