Table III. Clinical test/invesigation to diagnose diabetic neuropathy

Clinical test/investigation	Remarks
Ankle jerk	Large fiber neuropathy
128 Hz tuning fork vibration test	Large fiber neuropathy
10 g monofilament test	Loss of protective sensation, if abnormal response at one out of four sites
Biothesiometry	VPT ≥ 15 V abnormal
Autonomic function tests	Abnormal cardiovascular AFT act as surrogate for autonomic dysfunction in other organ systems
Nerve conduction studies	May not be able to detect small fiber neuropathy. Indicated mainly in atypical cases to differentiate from non-diabetic causes.
QSART	Detects sudomotor dysfunction, an early and sensitive marker of small fiber neuropathy
Sudoscan	Detects sudomotor dysfunction, an early and sensitive marker of small fiber neuropathy
Skin biopsy for IENFD	Mainly a research tool for detecting small fiber neuropathy.
Corneal confocal microscopy	Mainly a research tool for detecting small fiber neuropathy.
Nerve biopsy	Indicated in selected atypical cases

Abbreviations: IENFD: Intraepithelial nerve fiber density, QSART: Quantitative sudomotor axon reflex test, VPT: Vibration perception threshold

Table IV: Cardiovascular autonomic function tests

Test	Interpretation
Resting heart rate	>100/minute is abnormal
Beat to beat heart rate variation	In resting and supine position with respiratory rate of 6/min, monitor heart rate by ECG. HRV >15/min is normal and <10/min is abnormal. RR interval ratio during expiration and inspiration (E:I) <1.2 is abnormal
Heart rate response to standing	Measure R-R interval at 15 and 30 s after standing. 30:15 ratio <1.05 is abnormal
Heart rate response to Valsalva maneuver	Ratio of longest to shortest R-R interval should be >1.2
Diastolic response to isometric exercise	Following isometric exercise of 5 min using hand held dynamometer, rise of >16 mm Hg in contralateral arm is normal
Systolic response to standing	After 2 min of standing, a fall of <10 mm Hg is normal, 10-30 mm Hg borderline and >30 mm Hg abnormal
QTc measurement	>440 ms is abnormal

Abbreviations : ECG: Electrocardiogram, HRV: Heart Rate Variability

cells of rat sciatic nerves[13]. In a study from India involving 2190 subjects (90%, T2DM and 10%, T1DM) with DN and mean diabetes duration of 11.3 years, epalrestat (50 mg three times a day) administration for 3-12 months was associated with significant improvement in spontaneous pain, numbness, coldness and hypoalgesia, peroneal motor nerve- conduction velocity, sural sensory nerve-conduction velocity and vibration sensitivity[14]. Epalrestat was generally well tolerated, and adverse effects were noted in 2.5% of study participants, most common being hepatic dysfunction, and nausea and vomiting. Benfotiamine is a

transketolase activator that is known to reduce tissue levels of AGE and has been shown to cause improvement in neuropathy symptom score in two small studies involving 40 (BEDIP) and 165 (BENDIP) subjects with DN[15,16].

Management of painful neuropathy

Almost 25% of the patients with DN may have painful neuropathy. Painful neuropathy often causes impairment of sleep and compromises the quality of life. Hence, it is essential to treat painful neuropathy. An appropriate and effective drug should be chosen based on efficacy and tolerability by the individual patient. Treatment should be continued for at least 2-4 weeks before concluding that the drug is not effective. Since none of the drugs provide complete pain relief, a reduction of pain by 30-50% may be considered as a marker of effectiveness. In a Cochrane review of 61 RCTs, for tricyclic antidepressants (TCAs), the number needed to treat (NNT) for moderate pain relief was 3.6, while number needed to harm (NNH, defined as an adverse event leading to study withdrawal) was 28[17]. An ideal drug for neuropathic pain should have NNT close to 1 and NNH>10.

Pregabalin and gabapentin bind to α2δ-1 and α2δ-2 subunits of voltage-activated calcium channels, causing inhibition of cellular calcium influx and attenuation of neurotransmission, leading to reduction of neuropathic pain[18]. Pregabalin is the most extensively studied drug and has demonstrated positive result in most studies. It is approved by FDA for management of neuropathic pain in patients with diabetes. Common side effects of pregabalin and gabapentin include sedation, dizziness, ataxia and fatigue; peripheral edema and headache are more common with pregabalin. Side effects are more pronounced in elderly population. Hence, initiation with small dose (75 mg/day for pregabalin and 300 mg/day gabapentin) and gradual titration to maximum doses (300-600 mg/day for pregabalin and 900-1800 mg/day for gabapentin), as needed may be safer. It is important to note that drugs like pregabalin are to be used in adults with T1DM, as their use is off-label in children.

TCAs are also effective in reducing neuropathic pain but their use is limited by side effects. These include anticholinergic side effects (such as dry mouth, constipation, ocular side effects and urinary hesitancy), orthostatic hypotension and sedation. Side effects may be more pronounced in elderly people and hence TCAs should be used cautiously in them. Serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine are the other proven drugs for management of neuropathic pain. These agents effectively reduce neuropathic pain, while being associated with fewer side effects. The use of opioid agents (tramadol and extended release tapentadol) in the management of painful neuropathy is limited to third line due to their limited safety profile (abuse potential) and efficacy. The doses and side effect profile of commonly used drugs for the management of painful DN have been summarizedin Table V[19,20].

Midodrine, a α1-receptor agonist may be beneficial in the management of patients with orthostatic hypotension. Erectile dysfunction in men may be treated with phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil (50-100 mg) or tadalafil (5-20 mg). These agents are contraindicated in patients taking nitrates. In advanced cases where PDE-5 inhibitors are ineffective, transurethral prostaglandin (alprostodil) [medicated urethral system of erections (MUSE)], intracavernosal injections of prostaglandin E1, papaverine and phentolamine, vacuum constriction devices (VCDs), and penile prosthesis may be required. Short-term metoclopramide therapy should be considered

Table V: Commonly used agents for management of neuropathic pain, their dosages and adverse effects

Agent	Starting dose	Maximum dose	Adverse effects	Remarks
Gabapentinoids Pregabalin Gabapentin	25-150 mg OD 100-300 mg OD	150-300 mg BD 600-1200 mg TDS	Sedation, dizziness, visual blurring, peripheral edema, weight gain.	Dose adjustment needed in renal failure
TCAs Amitriptyline Nortriptyline	10-25 mg/d 10-25 mg/d	100-150 mg/d 100-150 mg/d	Sedation, dry mouth, confusion, constipation, urinary retention, orthostatic hypotension, blurred vision, mydriasis, fatigue, weight gain, arrhythmia	Contraindicated in patients with glaucoma, symptomatic prostatic disease and cardiovascular disease. Use with caution in elderly population.
SNRIs Duloxetine Venlafaxine	30 mg/d 37.5 mg/d	60-120 mg/d 150-225 mg/d	Sedation, dizziness, dry mouth, nausea, constipation, dyspepsia, ataxia	Exercise caution in patients with renal or liver disease
Opioids Tramadol Tapentadol (controlled release)	50 mg/d 50 mg BD	400 mg/d 500 mg/d	Sedation, dizziness, light-headedness, nausea, vomiting, constipation Sedation, nausea, vomiting, constipation	May lower seizure threshold. Exercise caution in patients with seizure disorder Exercise caution in patients with seizure disorder, liver or renal dysfunction

Abbreviations: BD: Twice daily, OD: Once daily, SNRIs: Serotonin and Norepinephrine reuptake inhibitors, TCAs: Tricyclic antidepressants, TDS: Thrice daily

in the management of diabetic gastroparesis. Management of various aspects of diabetic autonomic dysfunction has been discussed briefly in Table VI [21,22].

Prevention of diabetic foot

Foot examination should be done at each visit in patients with DN and at least annually in those without DN. Identification of foot at risk is the most important step in the prevention of diabetic foot ulcer. Patients with at risk foot should be instructed to take the following precautions:

1. Inspect feet yourself (with the help of mirror to inspect soles) or with the help of someone (especially when your vision is compromised) daily.
2. Wash feet daily with a non-medicated soap; pat feet dry with soft absorbent cloth especially between toes.
3. Apply lubricants containing urea or salicylates to the feet sparing the inter- digital spaces.
4. Wear footwear both indoors and outdoors. Wear only proper fitting shoes (not too loose

Table VI: Management of diabetic autonomic dysfunction

Condition	Treatment	Remarks
Orthostatic hypotension	Postural maneuvers, compression stockings, avoid hot water bath. Fludrocortisone (0.5-2 mg OD), Midodrine (2.5-10 mg TDS). Octreotide (0.1-0.5 µg/kg/day) may be helpful in preventing postprandial hypotension. Clonidine and erythropoietin have also been tried.	Can be easily diagnosed in clinic. Fall of systolic blood pressure without increase in heart rate is characteristic of orthostatic hypotension related to autonomic dysfunction.
Gastroparesis	Diet: Low fat, small frequent meals. Metoclopromide (10 mg TDS), Domperidone (10 mg TDS), Erythromycin (250 mg TDS), Levosulpride (25 mg TDS) (use 30-60 minutes before each major meal)	Rule out obstruction, (upper GI endoscopy), hyperglycemia, psychogenic vomiting.
Diarrhea	Diet: Soluble fiber Antimotility agents: Loperamide 2 mg TDS-QID or SOS Gut antibiotics: Metronidazole (400 mg TDS), Rifaximin (400 mg TDS) Bile salt sequesterants: Cholestyramine (4-12 g/d). Clonidine (0.1 mg BD-TDS) and Octreotide (50 µg BD-TDS) may also help in some cases.	Rule out infective etiologies (HIV serology, stool routine microscopy and culture), thyrotoxicosis, exocrine pancreatic dysfunction (stool elastase, 24-h fecal fat estimation, abdominal ultrasonography), gluten sensitive enteropathy (tissue transglutaminase antibody), bacterial overgrowth (hydrogen breath test), lactose intolerance, intrinsic GI disorders (inflammatory bowel disease, abdominal tuberculosis). Consider gastroenterology consultation.
Erectile dysfunction	PDE-5 inhibitors: Sildenafil (50-100 mg), Taldalafil (5-20 mg) 1 h before sexual intercourse. Intracavernosal or transurethral PGE1 therapy, vaccum constriction device, penile prosthetic pump may be required in cases not responding to PDE-5 inhibitors.	Rule out psychogenic, medication related, vascular and hormonal causes. Avoid PDE-5 inhibitors in patients on nitrates. Patients should be advised to avoid oily, heavy meal on the night of medication intake.
Cystopathy	Timed voiding, double or triple voiding, behavioural interventions, manual pressure (Credes maneuver). Cholinergic agent: Bethanechol 10 mg QID	Urine routine and culture tests, ultrasonography of KUB region, urodynamic studies may be needed. Consider urology consultation.
	Alpha blocker: Doxazosin 1-2 mg BD. Most advanced cases with hypocontractile bladder will need training on self CIC.	
Hypoglycemic unawareness	Relax targets for glycemic control, avoid hypoglycaemia	Recurrent hypoglycaemia may be associated with functional autonomic insufficiency
Sudomotor dysfunction	Foot care education, use of emollients and skin lubricants, anticholinergic glycopyrrolate (topical/oral) may be used in gustatory sweating	May be diagnosed with Sudoscan or QSART

Abbreviations: BD: Twice daily, OD: Once daily, TDS: Thrice daily, QID: Four times a day, QSART: Quantitative sudomotor axon reflex test, CIC: Clean intermittent catheterization, GI: Gastrointestinal, PDE-5: Phosphodiesterase-5, KUB: Kidney, ureter and bladder, PGE1: Prostaglandin E1; HIV: Human immunodeficiency virus

or too tight) and physically examine the inside of a shoe before wearing it. Shoes should have a broad toe box and preferentially be bought in evening hours.

5. Wear clean, cotton socks, preferably white colored (for easy detection of blood stains) with seams facing outwards. Avoid wearing tight socks and change socks on a daily basis.
6. Cut the toenails very carefully straight across and not in a rounded fashion or not too short.
7. Check for the warmth of water with hands/elbow before rinsing the feet with hot water.
8. Don't self-treat calluses or corns
9. If you notice any blisters, cracks, sore, discoloration or any unusual mark on the feet or if the feet get accidentally cut or injured in any way, contact a podiatrist immediately.

Summary

- Diabetic neuropathy is a chronic microvascular complication of diabetes, which may significantly affect patient's quality of life
- Diabetic sensorimotor polyneuropathy, a symmetric length dependent neuropathy is the most common form of diabetic neuropathy.
- Focal/multifocal neuropathies are less common but need diligent neurological examination and aid of electrophysiological tests to distinguish from non- diabetic causes.
- Diabetic autonomic neuropathy is a great mimic, effecting almost every organ system in the body.
- Cardiovascular autonomic function tests may act as surrogate for autonomic dysfunction involving other organ systems.
- Management of diabetic neuropathy includes achievement of good glycemic control, treatment of risk factors, pain management and foot care education.
- Despite clear understanding of its pathophysiology, no pharmacological agent which can alter the natural history of neuropathic process has been found successful till date.

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Chapter-9

Macrovascular Complications

Dr. Alpesh Goyal, Dr. Nikhil Tandon

Introduction

Patients with type 1 diabetes mellitus (T1DM) are at increased risk of morbidity and mortality from cardiovascular disease (CVD) compared to the non-diabetic population. This includes coronary artery disease (CAD), stroke and peripheral arterial disease (PAD), of which CAD is the most common. CVD remains a major cause of mortality in patients with T1DM and disease duration >20 years[1]. In patients with T1DM, cardiovascular (CV) events occur much earlier than in the general population. Most CV events occur more than two decades after the disease onset, implying a significant disease burden at a relatively young age (third and fourth decades of life)[2]. An early age at disease onset and a high CVD burden at a relatively young age has implications for potential loss of productive years of life and increased lifetime healthcare cost. There is also evidence to support increased severity of CVD in patients with T1DM; they are at a higher risk of having extensive disease (involving all the three major coronary arteries), distal vessel disease, and severe stenosis compared to subjects without diabetes[3].

The etiopathogenesis of CVD in T1DM is complex and mutifactorial, and will be discussed in detail in this chapter. With improving standards of care, and the resultant increase in the life expectancy of patients with T1DM, it is incumbent on the healthcare providers to appropriately understand and address the increasing burden of this long-term complication.

Epidemiology

In the Eurodiab IDDM Complications Study, > 3000 patients with T1DM (mean age 33 years and mean disease duration 15 years) were studied for CVD (defined by past history or presence of ECG abnormalities). The prevalence of CVD was reported to be 9% in males and 10% in females. The prevalence increased with age (6% in 15-29 years age group to 25% in 45-59 years age group) and duration of diabetes (6-9% in 1-7 years duration of DM to 13-15% in >15 years duration of DM)[4]. However, this study may have underestimated the actual CVD burden because patients with silent myocardial ischemia and inducible ischemia were not actively looked for. An important finding of this study (and confirmed by other studies) is that T1DM attenuates the protective effective of female sex (i.e., premenopausal age group) on CVD risk, which is usually seen in the general population [2,5]. As a result, relative risk compared to the general population is higher in females compared to males with T1DM. In the Allegheny County (PA) T1DM registry, the standardized mortality ratio (SMR) for total mortality (13.0 vs. 5.0) and CV mortality (24.7 vs. 8.8) was higher in females than males with T1DM[1].

Various prospective studies have also reported increased risk of CVD (CAD, stroke and PAD) in patients with T1DM, compared to the general population. UK General Practice Research Database (GPRD) comprised data from >7400 subjects with T1DM (mean age 33 years and mean disease duration 15 years) and >38000 subjects without DM, followed up for a mean duration of 4.7 years. The adjusted hazard ratio (HR) for CV events was reported to be 3.6 (95% CI, 2.9-4.5) in males and 7.6 (95% CI, 5.5-10.7) in females with type 1 DM. Besides, the CV event occurred 10- 15 years earlier in subjects with T1DM compared to the matched controls without diabetes. HR for CAD was reported to be 3.0 (95% CI, 2.2-4.1) in males and 7.6 (95% CI, 4.9-12.0) in females[6]. In the Nurses Health study, >100,000 women without diabetes and about 11,000 women with diabetes (both T1DM and T2 DM) were followed-up for a duration of 24 years. HR for fatal or non fatal stroke was reported to be 5.9 (95% CI, 4.2-8.2) in women with diabetes, compared to women without diabetes[7]. Patients with T1DM are also at higher risk of premature mortality after a stroke, compared to the general population. In the Finnish Diabetic Nephropathy study, 144 patients with T1DM who suffered a stroke were followed-up for a mean duration of 3.4 years[8]. Of these, 104 (72%) suffered a vascular composite end point (hard cardiovascular event or death from cardiovascular or diabetes- related cause), with an overall 1-year survival of 76% and 5-year survival of 58%. The presence of hemorrhagic stroke subtype and progression of diabetic kidney disease were predictors of worse outcome in the study cohort.

PAD, characterised by atherosclerotic occlusive disease of lower extremities, is a major risk factor for lower-extremity amputations. Its presence is also considered to be a surrogate marker for significant atherosclerotic burden in other vascular beds[9]. Like CAD and stroke, the risk of PAD and its adverse outcomes is significantly higher in patients with T1DM compared to the general population. However, due to its asymptomatic course, poor reporting of symptoms by the patient, attenuation of symptoms by the presence of neuropathy, and lack of a universal screening modality, PAD is often underreported in patients with diabetes[9]. In the Swedish Inpatient registry involving > 31,000 patients with T1DM followed for 12.5 years, HR for non-traumatic lower-extremity amputation (an outcome of PAD) compared to the general population was reported to be 85.5 (95% CI, 72.9-100.3)[10].

Risk factors and pathophysiology

1. Hyperglycemia

Poor glycemic control has been associated with increased risk of microvascular and macrovascular complications in patients with T1DM. In the Diabetes Control and Complications Trial (DCCT), >1400 subjects with T1DM were randomized to receive intensive or conventional glycemic control and followed-up for a mean duration of 6.5 years. Although microvascular benefits emerged in the intensive arm at the end of trial, no significant macrovascular benefits were seen. This could be attributed to the overall small number of cardiovascular events in a relatively young population, followed-up for a short duration[11]. However, in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up of the DCCT cohort, significant differences for macrovascular events emerged in favour of intensively treated arm despite closure of the glycemic gap between the two groups (legacy effect). At 17 years follow-up (DCCT/ EDIC combined), the overall risk of CVD events was reduced by 42% while the risk of

non-fatal myocardial infarction/stroke/cardiovascular death was reduced by 57% in the intensive arm compared to the conventional arm[12]. Also, the progression of carotid intima-media thickness (CIMT), a non-invasive marker of CVD was significantly lower in the intensive arm at six years after the end of DCCT[13]. The data from DCCT/EDIC therefore suggests that early intensive glycemic control may play a major role in reduction of future CV risk in T1DM patients.

Persistent hyperglycemia leads to increased generation of mitochondrial reactive oxygen species (ROS) and proinflammatory mediators through various pathways (Figure-1), resulting in endothelial dysfunction[14-16]. Healthy endothelium efficiently regulates vascular tone, thrombosis, leukocyte adhesion, platelet aggregation and inflammation. Hyperglycemia causes loss of vasodilatory, anti-inflammatory and anti-atherogenic properties of the healthy endothelium, leading to genesis of atherosclerotic CVD. In addition, uncontrolled diabetes is associated with other cardiovascular risk factors (such as dyslipidemia), as shown in the SEARCH for Diabetes in Youth study[17].

Acute hyperglycemia is also associated with poor post-stroke outcomes (both ischemic and hemorrhagic stroke)[18]. In patients with ischemic stroke, it increases cerebral lactate production and reduces the salvageable penumbral tissue, resulting in infarct expansion, while, in those with hemorrhagic stroke, it may cause expansion of hematoma and perihematomal edema. Optimal management of hyperglycemia is therefore extremely important in such patients.

2. Hypertension

Hypertension is a risk factor for microvascular as well as macrovascular complications in T1DM. The increased risk for CVD with hypertension occurs regardless of the presence of diabetic kidney disease (DKD)[2]. In the Coronary Artery Calcification in T1DM study (CACTI), involving 1416 subjects aged 19-56 years (652 T1DM subjects with mean age of 37 years and diabetes duration of 23 years, and 764 controls with mean age of 39 years) with no past history of coronary artery disease, hypertension was more common in subjects with T1DM than controls (43% versus 15%)[19]. Hypertension was better controlled in subjects with T1DM than controls, however, only 42% T1DM subjects met the target goal of <130/80 mmHg. In the SEARCH for Diabetes in Youth study involving >3600 patients with T1DM aged 3-17 years, hypertension was seen in about 6% of the study participants, predominantly affecting obese adolescents and those with poor glycemic control[20].

Hypertension in T1DM may occur as a result of DKD and obesity/insulin resistance. Poor glycemic control can also contribute to hypertension in the long-term. In the DCCT study, incident hypertension was not different in the two study arms, however during EDIC follow-up of the DCCT cohort, the risk of incident hypertension was found to be reduced by 24% (HR 0.76, 95% CI, 0.64-0.92) in the intensive arm compared to the standard treatment arm. In addition, higher glycated hemoglobin (HbA1c) at baseline or throughout follow-up was associated with increased risk of incident hypertension[21]. The landmark DCCT/EDIC study thus suggested that hyperglycemia may have a definitive role in the pathogenesis of hypertension; however, effects of intensive glycemic control on reduction of hypertension risk may appear in a delayed fashion (similar to the macrovascular complications).

3. Diabetic Kidney Disease (DKD)

DKD can manifest as microalbuminuria (albumin excretion rate (AER) 30-299 mg/ day), macroalbuminuria (AER ≥ 300 mg/day), and impaired glomerular filtration rate (GFR) (estimated GFR<60 ml/min/1.73m^2) with or without albuminuria. In various studies, DKD has been associated with graded increase in CV mortality from microalbuminuria to macroalbuminuria to end stage renal disease (ESRD)[2]. The presence of microalbuminuria is associated with about 4-fold higher risk of CVD and 2-fold higher risk for all cause and CV mortality[22-24]. Despite adjustment for potential confounders like dyslipidemia, hypertension and obesity (which accompany microalbuminuria), the risk of CV events remains significant, suggesting it to be an independent CVD risk factor. Microalbuminuria is, therefore, an early non-invasive marker for both DKD and CVD. In the EURODIAB study, the presence of macroalbuminuria was associated with a 9-fold higher risk of CV mortality[25]. Similarly, impaired GFR, regardless of albuminuria, is associated with increased CVD risk (with patients having ESRD at highest risk)[26,27].

Increased CV risk in patients with DKD could be a result of following factors: a) co-existence of other CV risk factors such as dyslipidemia, hypertension, obesity and insulin resistance, b) increased activity of renin-angiotensin-aldosterone system (RAAS), and volume retention due to DKD, c) anemia (common in patients with DKD, especially at low GFR) may contribute to left ventricular hypertrophy and dysfunction in the long-term.

4. Cardiac Autonomic Neuropathy (CAN)

CAN manifests as resting tachycardia, loss of heart rate variability, exercise intolerance, orthostatic hypotension and loss of nocturnal dip in blood pressure. Risk factors for CAN include poor glycemic control, hypertension, dyslipidemia and obesity[28]. CAN may be associated with silent myocardial ischemia and delayed presentation of CVD. In T1DM patients without CAD, CAN has also been related to impaired coronary flow reserve, which may predict future diastolic dysfunction[29]. In various studies, CAN has been shown to be an independent predictor of CV morbidity and mortality[30,31].

5. Dyslipidemia

As in general population, dyslipidemia is a risk factor for CVD in T1DM. While patients with normal body weight and well-controlled T1DM show lipid and lipoprotein concentrations similar to the general population, those with poor glycemic control/ obesity/insulin resistance tend to have an atherogenic lipid profile[32]. In the Search Diabetes for Youth study[17], among subjects with T1DM and poor glycemic control (HbA1c ≥9.5%), high concentration of total cholesterol (≥200 mg/dl), LDL-cholesterol (≥130 mg/ dl) and triglycerides (≥200 mg/dl) were seen in 35%, 27% and 12%, respectively. The corresponding numbers in patients with youth onset T2DM and poor glycemic control were 65%, 43% and 40%, respectively. Diabetic dyslipidemia is defined by the presence of elevated triglycerides, low HDL-cholesterol and predominance of LDL particles in the small dense form. The small dense LDL particles are more atherogenic because of their affinity to the arterial wall and susceptibility for oxidation, leading to recruitment of leukocytes, formation of foam cells and development of the atherosclerotic plaque. In addition, upon glycation, the half life of LDL particle is increased, while that of HDL particle is reduced, further worsening the atherosclerotic process[33].

6. Obesity and insulin resistance

The phenotype of patients with T1DM has evolved in the recent past, reflecting the increased rate of obesity in the general population. The adoption of unhealthy dietary practices and sedentary lifestyle coupled with improved glycemic control (less glucosuria) and at times, excessive eating for fear of hypoglycemia, may place these patients at increased risk of weight gain. In the DCCT/EDIC study, obesity prevalence increased from 1% at DCCT baseline to 31% at EDIC 12-year follow-up[34]. In particular, excessive visceral adiposity is associated with worsening insulin resistance, poor lipid control and increased CVD risk.

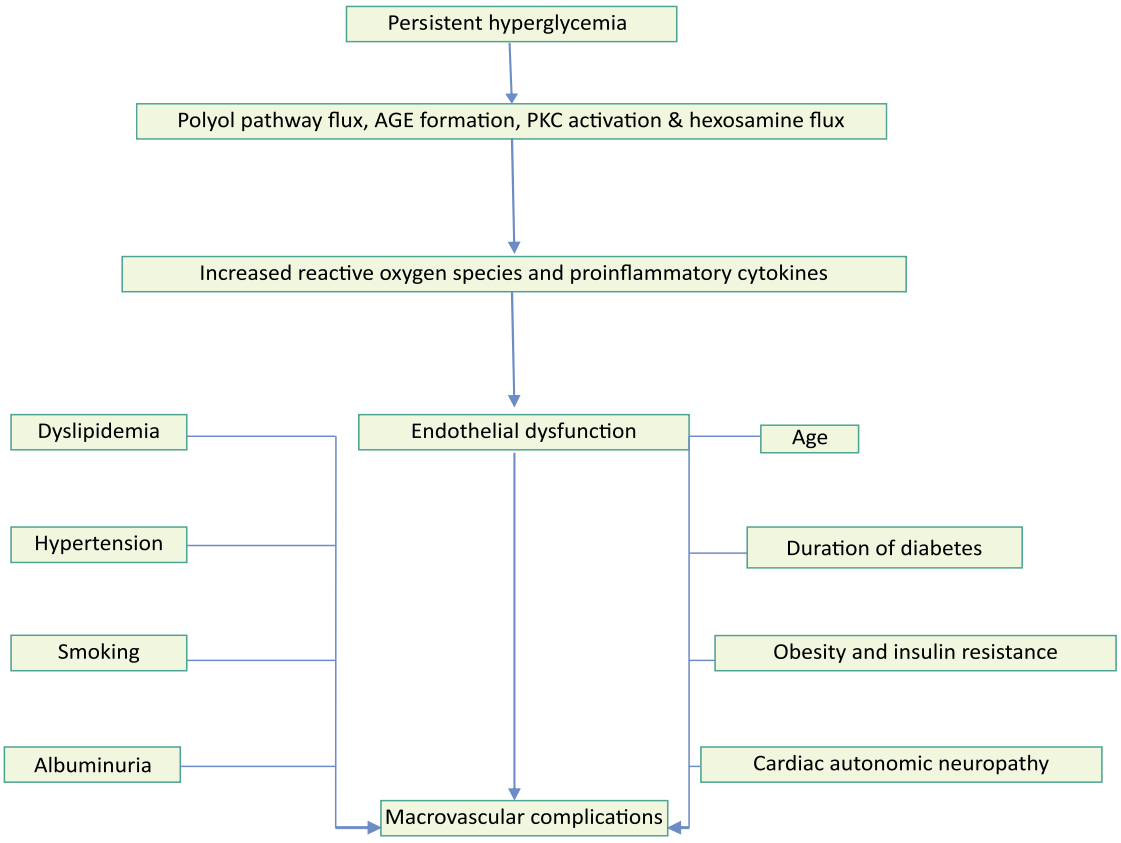
7. Smoking

Smoking is associated with increased risk of vascular complications-both microvascular and macrovascular. It increases CVD risk through unfavorable alterations in glucose and lipid metabolism, and development of endothelial dysfunction[35]. There is definite evidence to suggest reduction in CVD risk (particularly peripheral arterial disease) with smoking cessation[36].

8. Age and duration of diabetes

As discussed earlier, both increasing age and duration of diabetes are risk factors for CVD in T1DM population[4]. The pathophysiology of macrovascular complications in T1DM is illustrated in Figure-1.

Figure 1: Pathophysiology of macrovascular complications in patients with type 1 diabetes mellitus



Abbreviations: AGE- Advanced glycosylation end products; PKC-Protein kinase C

Cardiovascular risk factors in children and adolescents with T1DM

Although frank CVD may be rare in children and adolescents with T1DM, it is not uncommon to encounter clustering of CV risk factors in this population, placing them at high risk for future events. According to population-based studies, 14- 45% of children with T1DM have two or more cardiovascular risk factors[37-39]. In a study involving 283 children (median age 12.8 years) with T1DM (median duration 5.3 years), about 40% were found to be overweight/ obese. The overweight/ obese children were more likely to have hypertension (23.9% vs. 5.7%), metabolic syndrome (25.7% vs. 6.3%) and transaminitis (15.6% vs. 4.5%), compared to those with normal body weight[40]. With the rising prevalence of childhood obesity, these numbers are likely to increase in the future, posing tremendous challenges to the existing healthcare system.

Diagnosis/screening

Blood pressure and weight should be measured at each visit. In children, hypertension is defined as systolic or diastolic blood pressure ≥95th centile for age, sex and height on three or more occasions[41,42]. As per Center for Disease Control and Prevention (CDC), in childhood and adolescence, overweight is defined as body mass index (BMI) between 85th-95th centile for age and sex, while BMI ≥95th centile is considered as obesity[43]. On the other hand, the World Health Organisation (WHO) defines overweight and obesity as BMI ≥1 and 2 standard deviation (SD) above the mean for age and sex[44]. Since these BMI cut- offs are arbitrary and not related to specific health risk, there is a secular trend for increasing weight in populations worldwide (percentile or SD score based cut-offs may apparently normalize "childhood obesity") and because the increased risks of childhood obesity are mediated through tracking of obesity and related behaviors to adulthood, the International Obesity Task Force (IOTF) recommends the usage of BMI cut-offs which corresponds to adult BMI of 25 kg/m^2 (childhood overweight) and 30 kg/ m^2 (childhood obesity)[45]. Considering that at a given BMI, South Asians are at a higher risk for cardiometabolic disease, the recent Indian Academy of Pediatric guidelines recommend that BMI cut-offs 23 and 27 kg/ m^2 be used to define overweight and obesity, respectively in Indian children[46]. According to International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines, screening for dyslipidemia should be performed soon after diagnosis of T1DM (once blood glucose levels are stable) and if normal results are obtained, the evaluation should be repeated every 5 years[47]. Although a fasting lipid profile is ideal, a non-fasting lipid profile may be performed if the former is not feasible; if serum triglycerides or low-density lipoprotein cholesterol levels are elevated on a non-fasting study, a fasting lipid study may then be performed. Similarly, ISPAD recommends annual assessment of urinary albumin excretion in patients with T1DM beginning after the age of 11 years and 2-5 years of disease duration[47]. Routine screening for coronary heart disease beyond a resting electrocardiogram (ECG) is not recommended in patients with T1DM[2]. However, patients with symptoms of CVD or baseline resting ECG abnormalities (suggestive of ischemia) or those with clustering of multiple CV risk factors (intermediate or high risk on Framingham risk score or Reynolds risk score) should undergo a detailed assessment (Tables I and II). Of the various risk factors included in the Framingham risk score, age provides the most significant weightage. Both Framingham and Reynolds risk scores have been derived based on studies performed in older North American population[48-51], and their performance in young South Asian population with T1DM is not well understood[52].

Table I: Cardiovascular disease (CVD) assessment in patients with type 1 diabetes mellitus

Indications for detailed CVD assessment
Presence of symptoms of CVD
Baseline electrocardiogram suggestive of ischemia
Presence of multiple CV risk factors
Tools for CVD assessment
Exercise treadmill test (TMT) Dobutamine stress echocardiography
Dobutamine stress myocardial perfusion imaging (MPI)
Coronary artery calcification (CAC) by electron beam computerized tomography (EBCT)
Carotid intima media thickness (CIMT) Ankle-brachial pressure index (ABPI)
Endothelial dysfunction assessment by flow mediated dilation/brachial artery reactivity and Cardiac magnetic resonance imaging (MRI)

Table II: Components of cardiovascular disease risk prediction scores

Framingham risk score
Age
Sex
Total cholesterol
HDL-cholesterol
Smoking
Systolic blood pressure
Diabetes
Reynolds risk score
Age
Sex
Total cholesterol
HDL-cholesterol
Smoking
Systolic blood pressure
HbA1c, if person has diabetes
hs-CRP
History of MI in parents at age <60 years

Abbreviations: hs-CRP-High sensitivity C-reactive protein; MI-Myocardial infarction

Exercise treadmill test (TMT) remains the first line test for patients without peripheral neuropathy, foot deformity, previous amputation and baseline significant ST-T abnormalities, as it is cost-effective and easily available[2]. In patients who cannot undergo TMT due to above reasons, pharmacological stress testing (dobutamine stress echocardiography or dobutamine stress myocardial perfusion imaging (MPI)) may be performed. The use of pharmacological stress tests may, however, be limited by cost and availability.

Coronary artery calcification (CAC) is measured using electron beam computerized tomography (EBCT), and is an extremely helpful tool in quantifying the atherosclerotic plaque burden. CAC is scored as: 0-no plaque, 1-10-minimal, 11-100-mild, 101-400-moderate and >400-severe. CAC is seen at higher rates in patients with T1DM compared to the general

population and is more likely to progress in those with suboptimal glycemic control[53,54]. In the 10-year follow- up examination of Pittsburgh Epidemiology of Diabetes Complications Cohort, 302 adults with type 1 DM (mean age 38 years) underwent EBCT and clinical examination[55]. The prevalence of any CAC was reported to be 11% in participants with age <38 years and it increased to 88% in those with age 50-55 years. CAC was found to correlate with clinical CAD independent of other risk factors; however, the association was stronger in males compared to females. Also, a CAC score of >400 was found to be most efficient coronary calcium correlate of clinical CAD. In the CACTI study[19], CAC was seen in 39% males and 12% females with T1DM. Both men and women with CAC had higher age, BMI, waist circumference and waist-hip ratio, compared to those without CAC. CAC testing by EBCT has been suggested as an initial screening tool, followed by stress testing in those with CAC score >400[15].

Ultrasound guided CIMT measurement is another tool for CVD assessment. It has been proposed as a surrogate marker of early atherosclerosis; however, unlike CAC, the association between increased CIMT and subsequent CVD risk has not been studied in patients with T1DM. Hence, it is not recommended for routine clinical use. Ankle-brachial pressure index (ABPI) measured using hand- held Doppler device and sphygmomanometer is a standard tool for assessment of PAD. ABPI is ratio of systolic blood pressure of ankle (higher of the posterior tibial artery (PTA) or dorsal pedis artery (DPA) pressure on the given side) and arm (higher of the right or left brachial artery) and is interpreted as: normal (0.91- 1.3), mild ischemia (0.7-0.89), moderate ischemia (0.41-0.69) and severe or critical limb ischemia (<0.4). An ABPI value greater than 1.3 is also considered abnormal, suggestive of non-compressible vessels. Endothelial dysfunction can be assessed using flow mediated dilation/ brachial artery reactivity[56], and cardiac magnetic resonance imaging[57]; however, these are primarily research tools at present and not recommended for routine clinical use.

The utility of screening for asymptomatic CAD in diabetes was tested in two large randomised controlled trials (FACTOR-64 trial and The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study). In the FACTOR-64 trial, subjects with T1DM (n=108) and T2DM (n=791) with disease duration of at least 3-5 years and no CAD symptoms were randomized to screening with coronary computed tomography angiography (CCTA), followed by appropriate treatment or to standard care[58]. At a mean follow-up of 4 years, screening for asymptomatic CAD with CCTA failed to reduce the composite primary outcome of all-cause mortality, non fatal MI or unstable angina requiring hospitalization. Similarly, the DIAD study (included 1123 subjects with T2DM) found that the cumulative cardiac event rate over a follow-up of 4.8 years was not reduced by screening for asymptomatic CAD using myocardial perfusion imaging (MPI)[59]. Since these studies had few or no patients with T1DM, it may not be possible to provide a strong recommendation for or against screening for inducible ischemia in asymptomatic T1DM subjects; however, the limited evidence suggests that screening may not be required in asymptomatic individuals.

Prevention strategies

Macrovascular complications can be prevented if risk factors are addressed in a timely and appropriate manner. The role of glycemic control in etiopathogenesis of CVD has been proven beyond doubt by the landmark DCCT/EDIC trial. Optimal glycemic control (targeting HbA1c <7%), using multiple subcutaneous insulin injections (MSII) or insulin pump therapy (while minimizing iatrogenic hypoglycemia) should be attempted

in all individuals, especially those with short duration of diabetes and without other co-morbidities. Hypertension should be treated with angiotensin-converting enzyme inhibitor (ACE inhibitor)/angiotensin- receptor blocker (ARB) in combination with calcium channel blockers or thiazide diuretics, where needed. American Diabetes Association (ADA) recommends treatment to a target BP of < 140/90mm Hg, however, a target of < 130/80 mm Hg should be attempted in those where it can be achieved without additional treatment burden[2]. In patients with albuminuria, ACE inhibitor/ARB should be used regardless of hypertension in order to prevent further progression.

Diet and lifestyle modification along with optimization of glycemic control is recommended as the first line therapy for treating abnormal lipid levels. ISPAD clinical practice guidelines recommend dietary and lifestyle intervention for children and adolescents with T1DM and LDL-cholesterol >100 mg/dl; levels >130 mg/dl despite adequate dietary and lifestyle measures warrant institution of statin therapy in children aged 11 years or more[47]. Smoking cessation should be discussed actively and enrollment in smoking cessation program should be considered in selected cases. Finally, weight management is paramount and patients should be advised to engage in regular physical activity and consume a diet low in salt, saturated fat and simple sugars, and rich in fruits, green leafy vegetables, dairy products and fiber. A structured diet plan designed by a qualified dietician should be provided to each patient and body weight monitored periodically.

Patients with pre-existing CVD should receive lifelong statin (regardless of lipid levels), and antiplatelet agent (aspirin alone or aspirin plus clopidogrel combination for 12 months after acute coronary syndrome or percutaneous coronary intervention) as a secondary prevention strategy. Beta blockers should be added in those with previous myocardial infarction or left ventricular dysfunction.

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