In addition, interstitial fibrosis and tubular atrophy (IFTA) is graded based on the extent of interstitial involvement:

Score 0 : No IFTA
Score 1 : < 25% IFTA
Score 2 : 25 – 50% IFTA
Score 3 : > 50% IFTA

Glomerular and tubular basement membrane thickening with mesangial expansion is almost always present in DN. Kimmelstiel-Wilson lesion and Arteriolar Hyalinosis are often present in advanced disease while subendothelial hyaline "exudative" lesions and capsular drops, though rare, when present are characteristic of DN[17].

Podocytes maintain the integrity of the glomerular filtration barrier and are affected in diabetic kidney disease. Foot process effacement and decreased number of podocytes are seen in T1DM patients. Tubuloglomerular feedback results in hyperfiltration in diabetics; this tubular dysfunction contributes to albuminuria due to defects in lysosomal uptake and processing. Extensive studies are needed to understand the respective roles of tubuloglomeular feedback and podocytes in progression of diabetic kidney disease.

Differentiation from non-diabetic renal disease

Nondiabetic renal disease (NDRD) is rare in patients with T1 DM, unlike in type 2 diabetes, with a reported incidence of 2 – 3% among those with renal disease. The classical pointers for NDRD are presence of hematuria, rapidly deteriorating renal function, sudden onset of gross proteinuria, shorter duration of diabetes and absence of other microvascular complications (especially retinopathy)[18]. The presence of these features necessitates the requirement for kidney biopsy to establish the cause for kidney disease. Once the patient has had diabetes for over 30 years without any end organ involvement, it is very rare for the patient to develop diabetic nephropathy.

Diabetic patients can be afflicted with other renal diseases too. Patients with diabetes are at increased risk for atherosclerosis and consequently renal artery stenosis, which presents as difficult to control hypertension with episodes of flash pulmonary edema and progressive renal function. Papillary necrosis can occur in the setting of urinary tract infections or intake of nonsteroidal anti-inflammatory drugs. These patients present with hematuria, flank pain and fever. Diabetes results in a hyporeninaemic state with hypoaldosteronism and can present with hyperchloremic metabolic acidosis and hyperkalemia.

Screening and diagnosis

The diagnosis of diabetic nephropathy rests on the measurement of albuminuria and renal function. An annual assessment has to be done in all T1DM with disease duration of 5 years or more. The traditional model of diabetic kidney disease consists of three sequential stages – that of microalbuminuria followed by overt proteinuria, which is followed by progressive CKD culminating in ESRD. This was the basis for the therapeutic strategy of using renin angiotensin aldosterone system (RAAS) blockade to prevent progression of DN by controlling albuminuria.

Diabetic nephropathy is diagnosed by the presence of persistent albuminuria of > 300 mg/24 hours or an albumin-creatinine ratio (ACR) of > 300 mg/g in 2 out of

3 samples usually in the presence of diabetic retinopathy with no other obvious kidney disease. Microalbuminuria (30 – 300 mg/g) is the earliest detectable marker of DN. Screening for MA should be done yearly to detect renal involvement at an early stage. Early morning spot urine assessment is sensitive screening tool for MA. Due to issues with standardisation of tests and day-to-day variability, at least 2 spot samples in a period of 6 months are required to confirm the diagnosis of persistent MA. Alternatively, a 24-hour urine collection can be done for confirmation. The definition for albuminuria in diabetic kidney disease is provided in Table II[19].

Table II: Definition of albuminuria in diabetic kidney disease

Terminology	Definition
Normoalbuminuria	Urinary albumin < 20 µg/min or < 30 mg/24 h or ACR < 30 mg/g
Moderately increased albuminuria (Microalbuminuria)	Urinary albumin of 20 to 200 µg/min or 30 to 300 mg/24 h or ACR of 30 – 300 mg/g
Severely increased albuminuria (Macroalbuminuria)	Urinary albumin of > 200 µg/min or > 300 mg/24 h or ACR > 300 mg/g

Abbreviation: ACR- albumin creatinine ratio

Renal function assessment is done using serum creatinine based eGFR calculation. The most widely used formula is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae. Derangements in renal function usually accompanies worsening albuminuria in diabetic patients, the only exceptions being the non-albuminuric phenotype wherein renal dysfunction progresses without albuminuria.

The future for recognising patients at risk for DN and its progression depends on the "omics" platforms. Genomic studies are expected to throw light on susceptibility genes. Transcriptomics on renal biopsy specimen may aid in identifying progressors. The discovery of the role of JAK-STAT pathway and the probable role of its inhibitor in managing DN is a testimony for the future role of transcriptomics in DN. Metabolomic profiling of urine and serum samples have shown some promise in T2DM. Urinary proteomics of peptide profile in urine can identify cases at high risk for progression of kidney disease. The Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention of Early Diabetic Nephropathy in Type 2 Diabetic Patients with Normoalbuminuria (PRIORITY) is a study in progress to classify high risk patients based on proteomic analysis. The use of "omics" in DN will pave the way for personalized medicine in the future[19]. Neutrophil gelatinase associated lipocalin (NGAL), plasma growth differentiation factor 15, chitinase-3-like protein 1 are some new biomarkers being evaluated to identify early diabetic kidney disease before microalbuminuria sets in.

Overview of management, referral and follow up plan

The mainstay of management of DN focusses on glycemic control, antihypertensive therapy, lipid lowering drugs and dietary protein restriction. The aim of therapy is to prevent progression from normoalbuminuria to microalbuminuria (primary prevention), microalbuminuria to overt nephropathy and CKD (secondary prevention).

Primary prevention

Glycemic control is quintessential to prevent complications of diabetes be it type 1 or type 2. Any duration of strict blood glucose control preserves GFR, takes care of hyperfiltration

injury and hyperperfusion. Even 3 weeks of intensive therapy tends to improve the renal hemodynamics and consequently renal prognosis[20]. The DCCT study showed that MA reduced by 39% (95% CI, 0.21 to 0.52) and albuminuria reduced by 54% (95% CI, 0.19 to 0.74) in the intensive arm. On follow up in the EDIC study, the intensive arm had 50% reduced risk (95% CI, 0.18 to 0.69; P = 0.006) for worsening kidney disease[15]. Long term intensive blood glucose control has shown to reduce the odds for progressing from normoalbuminuria to microalbuminuria by 0.22 to 0.40[21].

Glomerular hypertension is a major factor for DKD and reducing the intraglomerular pressure is expected to be beneficial for the kidney. Among normotensive, normoalbuminuric TIDM patients, the Renin Angiotensin System Study (RASS) compared the efficacy of Angiotensin receptor blocker (ARB), ACE inhibitor and placebo over 5 years[22]. The trial failed to show any benefit for RAAS blockade with regard to nephropathy and albuminuria. However, there was a significant reduction in incidence of diabetic retinopathy. This was also shown in the DIRECT study wherein candesartan reduced the incidence (but not progression) of retinopathy with no beneficial effects on albuminuria incidence[23]. This is in contrast to T2DM where RAAS blockade has shown to reduce the incidence of microalbuminuria in multiple studies. One explanation could be that the trials in T2DM had hypertensive patients while the T1DM patients were normotensive. At present evidence base does not suggest the use of ACEi/ARB in normotensive normoalbuminuric diabetic patients.

Secondary prevention

Secondary prevention relies on the fact that multimodal intervention targeting risk factors for progression of DN will help revert the changes of DN. The most important element is optimal blood glucose control. Studies on patients with pancreatic transplantation revealed reversal of glomerulopathy with 5 years of normoglycemia. The time duration of normoglycemia or intensive glucose control to reverse the end organ damage in diabetes stays uncertain. There are no studies to show the direct effect of glycemic control on secondary prevention in T1DM.

Antihypertensive therapy with RAAS blockade has been shown to delay the progression of MA to overt nephropathy and CKD in T1DM patients. Though blood pressure targets are based on studies in type 2 diabetes, the general recommendation from American Diabetic Association (ADA) is to target a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg[24]. A lower target of <130/80 mmHg is suggested for those with high risk of cardiovascular disease. A recent meta-analysis in T1DM patients showed that RAAS blockade has a long-lasting effect on preventing progression to overt nephropathy with significant reduction in albuminuria. The risk of macroalbuminuria (from MA) was reduced significantly (OR 0.38; 95% CI, 0.25 to 0.57)[25].The cost effectiveness of early screening and RAAS blockade has also been demonstrated by various studies.

Overt nephropathy

The primary aim of therapy in established diabetic nephropathy is to prevent progression of kidney disease to ESRD. Early initiation of therapy focussing on albuminuria reduction has long lasting beneficial effects on renal function. This was obvious in the study by Parving et al where early therapy improved both albuminuria and renal function in T1DM. The Captopril Collaborative Study Group demonstrated a remarkable reduction in risk of doubling of serum creatinine in T1DM patients treated with captopril (48%; 95% CI, 16 to

69%)[26]. Regression of DKD is seen in those on intensive antihypertensive therapy. There was an additional benefit for RAAS blockade in addition to the one obtained by routine antihypertensive therapy for blood pressure control.

The effects of RAAS blockade varies in patients due to interpatient variability of RAAS. This can be explained by the role of ACE gene polymorphism. Individuals with T1DM with homozygous II polymorphism have been shown to respond better to RAAS blockade. This was proven in the EUCLID study wherein patients with II genotype had 57% reduction with lisinopril as against 17% in the ID group and 19% in the DD group[27]. The DD genotype is associated with more rapid loss of renal function and warrants more aggressive RAAS blockade. Direct comparisons between ACEI and ARBs have shown that they offer similar short-term and long- term renoprotection. The optimal daily ARB dosage for maximum anti-proteinuric effect is 100 mg for losartan, 320 – 640 mg for valsartan, 80 mg for telmisartan, 128 mg for candesartan and 900 mg for irbesartan[28]. Though most patients achieve optimal response at standard dosage, some patients require supra-maximal dose for best results. Combined RAAS blockade is not advised as apart from minimal improvement in albuminuria control, none of the trials have exhibited substantial renoprotection or cardio protection.

The prognosis for diabetic nephropathy in T1DM has improved notably during the past three decades. Prior studies reveal a poor prognosis for patients with diabetic nephropathy with a median survival of 5 – 7 years and ESRD being the most important cause of death in 66% of patients. With the regular use of antihypertensive therapy in the 1970s, the mortality rate dropped to 18% at 10 years of diabetic nephropathy. The Collaborative Study Group showed that captopril reduced the risk for death or progression to ESRD by 61% (95% CI, 26 to 80%, P = 0.002)[26]. In one of the recent prospective study by Astrup et al, the median survival in DN was 21 years, a noteworthy improvement over the years[29].

Other treatment options

The therapeutic armamentarium in DN is limited. The effects of lipid lowering therapy on progression of DKD are variable and inconclusive. At present, statin therapy is recommended in diabetic patients with CKD stages 1-4 by the ADA and it can be continued in ESRD if the patient is already on therapy.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors block the SGLT2 transporter in the proximal renal tubule. This causes glucosuria, natriuresis and improves glycemic control in T2DM. The renoprotective and cardioprotective effects of SGLT2i in T2DM has been now proved beyond doubt. Hence, the question arises as to whether they can be used to prevent complications in T1DM. Some reports have suggested that SGLT2i use is safe in T1DM apart from the risk of diabetic ketoacidosis. Further long-term studies are required before they can be recommended for routine use in T1DM[30].

Dietary protein restriction (0.6 to 0.8 g/kg/day) reduces glomerular hyperfiltration and consequently albuminuria. In a prospective study of T1DM patients with progressive nephropathy it was seen that over 4 years, only 10% of patients on a low-protein diet progressed to ESRD as against 27% on a normal protein diet conferring a relative risk of 0.23 (95% CI, 0.07 to 0.72)[31].The present Kidney Disease Outcome and Quality Initiative (KDOQI) guidelines recommend a protein intake of 0.8 g/kg body weight/day for CKD patients of stages 1 to 4.

Vitamin D analogues have shown some promise in diabetic nephropathy in conjunction with RAAS blockade but further studies are required before any recommendation can be made. Soludexide, a glycosaminoglycan combination and Tranilast, an antifibrotic agent have been tried to prevent progression of DKD.

In patients who have progressed to ESRD, renal transplantation offers the best survival advantage and quality of life. Though people with diabetes in general have a poorer outcome than those without disease, the advantage of transplantation over dialysis is still significant in them. With the advent of better powerful immunosuppressants, combined kidney-pancreas transplantation is increasingly associated with better glycemic control, improved survival and better cardiovascular outcomes.

Conclusions

Diabetic nephropathy is a serious complication of T1DM associated with significant morbidity and mortality. Though the pathogenesis is multifactorial, hyperglycemia is the predominant inciting factor and early optimal glucose control ensures best prognosis. Screening and diagnosis depend on assessment of albuminuria and renal function which has to be done annually once the disease duration is five years or more. Non-albuminuric phenotype of DN needs to be thought of when isolated renal dysfunction is present. Though microalbuminuria has long been considered a reliable and the earliest marker of diabetic nephropathy, it can be temporary or transient and patients may have associated renal dysfunction even at diagnosis. Newer biomarkers and use of advanced "omics" technology may pave the way for earlier diagnosis and personalized management in the future. At present, management consists of adequate glucose control, optimal blood pressure management with RAAS blockade and close follow-up. The future research in DKD focusses on early screening and diagnosis with better preventive measures for protection from adverse renal and cardiovascular outcomes.

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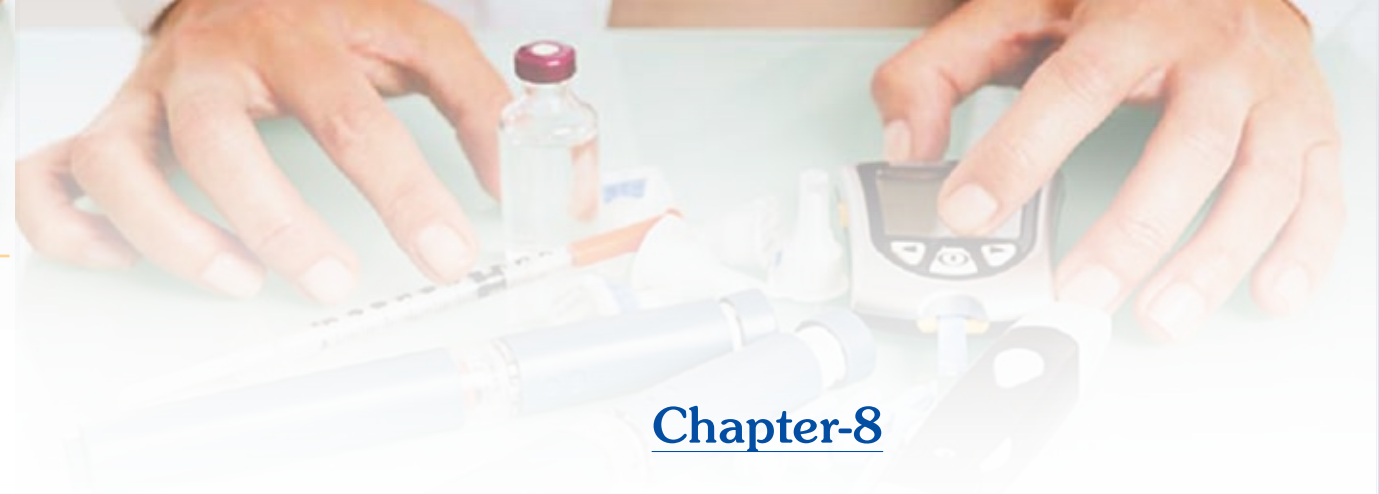

Chapter-8

Microvascular Complications - Neuropathy

Dr. Vijayasarathi HA, Dr. Unnikrishnan AG

Epidemiology

Neuropathy is a common microvascular complication in patients with type 1 diabetes mellitus (T1DM) which is associated with significant morbidity and mortality. It is the most important contributing factor for the development of foot ulcers and lower extremity amputations. The prevalence of neuropathy in T1DM varies from 7% to 57% in smaller studies, depending on the criteria used to define it. Data from Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study suggest that at least 20% of patients with T1DM develop distal symmetric polyneuropathy (DSPN) by 20 years from the onset of diabetes[1]. Similar prevalence rates are also reported for cardiac autonomic neuropathy (CAN). In a systematic review and meta-analysis, the pooled prevalence of peripheral neuropathy was higher in subjects with T1DM in>16-yr age group compared to those in < 16-yr age group (59.1% vs. 9.5%) and in those with duration of diabetes >10 years compared to those with disease duration of <10 years (35.0% vs. 9.4%)[2]. In a long-term follow-up study involving 27 subjects with T1DM and mean diabetes duration of 40 years, small fiber and large fiber neuropathy were reported in 22 (81%) and 16 (59%) participants, respectively[3].

There is a paucity of data on the prevalence of microvascular complications in Indian patients with T1DM. In a multicenter study by Unnikrishnan and colleagues involving 535 subjects with T1DM with a mean diabetes duration of 5.6 years, the prevalence of neuropathy was reported to be 6%[4].

Pathogenesis

The factors contributing to development of neuropathy in individuals with diabetes are not completely understood. Multiple hypotheses have been proposed and it is believed that diabetic neuropathy (DN) is a multifactorial process. The most important factor in the pathogenesis of neuropathy in patients with T1DM is hyperglycemia whereas minor contributions are microvascular insufficiency and autoimmunity. The fact that hyperglycemia plays a pivotal role in pathogenesis of DN is evident from the results of DCCT trial, wherein benefits of intensive glycemic control persisted even >10 years after the study completion (metabolic memory). Hyperglycemia contributes to the development of DN by multiple mechanisms such as increased polyol pathway flux, AGE formation and PKC activation[5].

Increased polyol pathway flux

High concentration of intracellular glucose shunts the excess glucose into polyol pathway leading to increased production of sorbitol and fructose by the enzymes aldose reductase

and sorbitol dehydrogenase, respectively. Accumulation of these impermeable substances leads to osmotic stress and efflux of other osmolytes such as myoinositol, taurine and adenosine. The decrease in myoinositol reduces the formation of ATP and in turn, reduces the activity of Na^+/K^+/ATPase leading to impaired axonal transport. Utilization of NADPH during aldose reductase-mediated conversion of glucose to sorbitol results in a shortage of NADPH required for regeneration of reduced glutathione (GSH), which in turn causes oxidative stress.

Increased advanced glycation end products

There is increased formation of advanced glycation end (AGE) products in intracellular and extracellular compartments. Increased intracellular AGE formation occurs due to nonenzymatic reaction of excess glucose with proteins and nucleotides which leads to impairment of neurotropic support and repair mechanisms. AGE also increases the glycation of mitochondrial proteins including enzymes of oxidative phosphorylation and alters their function leading to oxidative stress. Increased extracellular AGE formation causes activation of receptors for advanced glycation end products (RAGE) and stimulates an inflammatory response by activating nuclear factor kappa B (NF-kB).

Activation of Protein Kinase C pathway

Increased diacylglycerol formation leads to activation of protein kinase C (PKC) β and δ isoforms. The role of PKC pathway activation in the pathogenesis of DN is not clear. The limited data suggests that PKC activation may reduce nitric oxide (NO) production and increase endothelin-1 activity leading to reduced nerve blood flow; it may also reduce Na^+/K^+/ATPase activity, resulting in decreased nerve conduction and nerve regeneration. The role of hexosamine pathway activation in the pathogenesis of DN is less explored.

Increased oxidative stress

Increased glycolysis and TCA cycle activity produces an over-abundance of NADH and FADH2 electron donors leading to a high proton gradient across the inner mitochondrial membrane, which disrupts oxidative phosphorylation and, in turn, markedly increases reactive oxygen species (ROS) production. This increased ROS production is in fact, the primary inducing process of each of the above described different mechanisms.

Autoimmunity

Although not definitive, there have been some evidences to suggest a role for autoimmunity in the pathogenesis of DN. Autoimmune neuropathies like chronic inflammatory demyelinating neuropathy (CIDP) and vasculitis are significantly more common in both T1DM and T2DM subjects and account for a large proportion of proximal neuropathies in these patients. In a retrospective health insurance administrative claims database study, the prevalence of CIDP in in a patient population with diabetes was found to be 9-fold higher compared to a patient population without diabetes (54 per 100,000 persons vs. 6 per 100,000 persons)[6]. Similarly, in a hospital-based study, Sharma et al reported that the odds of occurrence of CIDP were 11-fold higher in subjects with diabetes compared to those without diabetes[7]. While an occurrence of CIDP is reported to be equal in T1DM and type 2 diabetes mellitus (T2DM) by some investigators[7], others have reported it to be more frequent in T2DM[8].

Risk factors

Duration of diabetes and severity of hyperglycemia are the two most important risk factors for development of DN[9]. Features of insulin resistance such as dyslipidemia

(especially elevated triglycerides) and high blood pressure are additional risk factors. Smoking contributes significantly to the development of DN[10]. Besides, exposure to toxic substances like alcohol may enhance the development of DN. Patients with other microvascular complications such as microalbuminuria and retinopathy are at a higher risk of DN. Height may be an independent predictor since DN is a typical length dependent neuropathy. Recent evidences also favor a role of genetics in the development of DN.

Clinical features and staging

DN is defined as the presence of signs and/or symptoms of peripheral neuropathy in a patient with diabetes, after other causes of neuropathy have been excluded. The clinical presentation of DN is varied, depending on the type, duration and extent of neuropathy. Symptoms are often mild and frequently go unnoticed in the initial stages. It is mainly classified into diffuse neuropathy (>90%) and focal/multifocal neuropathy (<10%) (Table I). Focal/multifocal neuropathies are generally characterized by acute/subacute onset, focal deficits, presence of pain and spontaneous partial/complete recovery. These have been described more commonly in older patients with T2DM and may co-exist with the prototypical distal symmetrical polyneuropathy (DSPN) in a given patient.

Table I: Classification of diabetic neuropathy

I. Diffuse neuropathy (>90%)
A. Distal symmetric polyneuropathy (DSPN)
- Primarily small-fiber neuropathy
- Primarily large-fiber neuropathy
- Mixed small- and large-fiber neuropathy

B. Autonomic neuropathy
- Cardiovascular
- Gastrointestinal
- Urogenital
- Sudomotor dysfunction
- Hypoglycemia unawareness
- Abnormal pupillary function

II. Focal or multifocal neuropathy (<10%)
A. Mononeuropathy
B. Isolated cranial or peripheral nerve neuropathy
C. Mononeuritis multiplex
D. Radiculopathy
E. Lumbosacral polyradiculopathy (proximal motor amyotrophy)
F. Thoracic radiculopathy

Diffuse neuropathy

Distal symmetric polyneuropathy

DSPN is the classical presentation of neuropathy in patients with diabetes. It can present as predominantly small fiber or large fiber neuropathy or more commonly as mixed small and large fiber neuropathy. DSPN is a typical length dependent polyneuropathy and hence, the initial symptoms and signs manifest in the feet and legs; as neuropathy progresses, the lower limb affection extends up to knees and hands are also affected.

Small fiber neuropathy

Small fiber neuropathy occurs due to involvement of unmyelinated C fibers and thinly myelinated Aδ fibers. Positive symptoms predominate and include burning, or lancinating pain (C fiber pain) often accompanied by hyperalgesia, dysesthesia and allodynia. As the disease progresses, numbness and hypoalgesia may occur. Hence, disappearance of pain should not always be interpreted as recovery of neuropathy and most often it reflects the progression of neuropathy, making the feet vulnerable to infection Loss of pinprick

sensation is a simple objective test for small fiber neuropathy. Abnormal thermal sensation is an additional manifestation of small fiber neuropathy.

Small fiber DSPN is also characterized by autonomic dysfunction in the feet with decreased sweating, dry skin, impaired blood flow and cold feet. Motor functions are usually preserved with intact motor strength and deep tendon reflexes. Since small fibers contribute less towards nerve conduction velocity (NCV), small fiber dysfunction may not be detected by routine nerve conduction studies. Sweat glands are innervated by unmyelinated sympathetic C fibers and abnormality of sweat gland innervation, that is, sudomotor dysfunction is an early and sensitive marker for small fiber neuropathy. Sudomotor dysfunction can be detected by: a) quantitative sudomotor axon reflex test (QSART) which measures postganglionic sympathetic cholinergic function. QSART involves iontophoresis of acetylcholine to produce local sweating which is quantified by a sudorometer, and b) electrochemical skin conduction test (Sudoscan) which is based upon the principle of reverse iontophoresis. This test involves application of low voltage current which attracts chloride ions from sweat gland, and an electrochemical reaction occurs between chloride ions in sweat and stainless steel based plate electrodes, on which patient's palm and sole (areas with highest sweat gland density) are placed. Reduced intra epidermal nerve fiber density (IENFD) on skin biopsies (3 mm punch) is also a good test for the early diagnosis of small fiber neuropathy. However, it is not recommended in routine practice. An alternative emerging non-invasive testfor the early diagnosis of small fiber neuropathy is corneal confocal microscopy (CCM).

Treatment induced neuropathy of diabetes (TIND) is a rare iatrogenic form of small fiber neuropathy which results from abrupt intensification of glycemic control in a patient with chronic hyperglycemia. This condition can occur subsequent to treatment with either insulin or oral glucose lowering drugs, and hence, the term "insulin neuritis" used previously for this condition is not preferred. TIND is associated with severe pain and is often accompanied by hyperalgesia and allodynia; fortunately this condition is rapidly reversible and remits in less than 6 months in most cases.

Large Fiber Neuropathies

In large fiber neuropathy, large myelinated, rapidly conducting Aα/β fibers (which serve sensory as well as motor function) are affected. Symptoms may be minimal and include numbness (sensation of walking on cotton, floors feeling "strange") and tingling without pain. Large fiber neuropathy is a disease of signs which include impairment of vibration perception (often the first objective evidence, 128-Hz tuning fork), light touch perception (reduced sensitivity to 10 g Semmes Weinstein monofilament) and joint position perception and presence of sensory ataxia. Initial motor system abnormalities include abnormal deep tendon reflexes (ankle reflex) and wasting of small intrinsic muscles of feet with hammertoe deformities. Large fiber neuropathy increases risk for falls, fractures, and development of Charcot neuroarthropathy.

Grading of DSPN severity

The severity of DSPN can be estimated by the staging system provided by Dyck[11]:

- Grade 0 = Normal nerve conduction (NC)
- Grade 1a = Abnormal NC without symptoms or signs
- Grade 1b = Abnormal NC plus signs of DSPN but no symptoms

- Grade 2a = Abnormal NC plus symptoms of DSPN with or without signs
- Grade 2b = Abnormal NC plus a moderate degree of weakness (i.e., 50%) of ankle dorsiflexion with or without DSPN symptoms.

Autonomic neuropathy

Identification and appropriate management of autonomic neuropathy is essential since it improves symptoms, reduces sequelae and improves quality of life. Clinical manifestations of diabetic autonomic neuropathy have been summarized in Table II.

Table II: Clinical manifestations of diabetic autonomic neuropathy

Organ system	Clinical manifestations
Cardiovascular	Resting tachycardia, orthostatic hypotension, exercise intolerance, heat intolerance, cardiac denervation with fixed heart rate, painless myocardial infarction, cardiac arrhythmia, intraoperative cardiovascular instability, increased risk of sudden cardiac death
Gastrointestinal	Esophageal dysmotility, gastroparesis, constipation, nocturnal diarrhea, fecal incontinence
Genitourinary	Erectile dysfunction, retrograde ejaculation, vaginal dryness, female sexual dysfunction, diabetic cystopathy, neurogenic bladder
Metabolic	Hypoglycemic unawareness
Pupillary	Argyll-Robertson pupil, impaired dark adaptation, difficulty driving in night
Sudomotor	Hypohidrosis involving the lower extremities, gustatory sweating

Cardiac autonomic neuropathy

Presence of CAN increases the risk of cardiovascular disease (CVD). In the early stages, CAN is usually asymptomatic and reduced heart variability during deep breathing may be the only abnormality. In advanced cases, resting tachycardia and orthostatic hypotension may be demonstrable. CAN is associated with increased mortality and sudden death (malignant arrhythmias). In patients with CAN, intensification of blood glucose and blood pressure control may increase the risk of a cardiovascular event.

Gastrointestinal autonomic neuropathy

Gastrointestinal autonomic neuropathies may affect any portion of gastrointestinal tract. Esophageal dysmotility, gastroparesis (gastropathy), enteropathy (diarrhea), colonic hypomotility (constipation) and fecal incontinence are among the major manifestations of gastrointestinal autonomic neuropathy. It is important to note that acute diabetic gastroparesis may occur in patients with severe hyperglycemia, and is reversible. Chronic gastroparesis is the result of autonomic neuropathy and may manifest with upper abdominal symptoms like postprandial fullness or glycaemic fluctuations.

Genitourinary autonomic neuropathy

The manifestations of genitourinary autonomic dysfunction include urinary incontinence and diabetic cystopathy (neurogenic bladder) which usually manifests as nocturia, frequent urination, urination urgency, and weak urinary stream. Genital dysfunction in men may manifest as erectile dysfunction and retrograde ejaculation, whereas female sexual dysfunction may manifest as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication.

Sudomotor dysfunction

It may manifest as hypohidrosis/anhidrosis of the lower part of the body where nerves are dying. This may lead to fissure and cracks over the skin, culminating into increased risk for foot ulceration. It may also manifest as hyperhidrosis of the upper body where nerves are still preserved. Gustatory sweating which manifests as increased sweating of the face especially during consumption of hot and spicy food could be another manifestation of sudomotor dysfunction in DN patients. Autonomic neuropathy also plays an important role in the pathophysiology of Charcot neuroarthropathy by causing an increase in peripheral blood flow through opening of arteriovenous shunts, thus resulting in increased bone resorption.

Focal and multifocal neuropathy

Cranial neuropathy

It manifests with acute isolated involvement of cranial nerve III, VI, VII, of which cranial nerve III is most commonly involved (diabetic ophthalmoplegia). Diabetic ophthalmoplegia presents with ptosis, diplopia and orbital pain. Peripheral pupillary fibers are often spared, as opposed to surgical causes of III nerve palsy. However, about 15% cases of diabetic ophthalmoplegia may have pupillary involvement and need exclusion of surgical causes like aneurysm and neoplasms.

Entrapment neuropathy

A number of peripheral nerves (such as median, ulnar, radial, lateral cutaneous nerve of thigh and peroneal nerve) are prone to pressure damage in patients with diabetes. Among these, median nerve is most commonly involved as it passes under the flexor retinaculum, leading to carpal tunnel syndrome.

Truncal radiculopathy

The common presentation is pain in dermatomal distribution in the region of chest/abdomen and asymmetric bulge in abdomen due to weakness of abdominal muscles. The common differentials are herpes zoster and spinal nerve root compression. This condition shares striking similarities with diabetic amyotrophy in terms of significant pain, asymmetry, weight loss and morbidity.

Proximal motor neuropathy

This condition presents with severe pain in the region of thigh or lower back with associated weakness and wasting in proximal lower limbs. The involvement is asymmetric and even if bilateral, one limb is clearly affected to a greater degree. It is also called as diabetic amyotrophy or diabetic lumbosacral radiculoplexus neuropathy (DLRPN). The condition is associated with weight loss, depression and poor glycemic control, and improves over a period of months-years in most cases. Common differentials include chronic inflammatory demyelinating polyneuropathy (CIDP), monoclonal gammopathy of undetermined significance (MGUS) and inflammatory vasculitis.

Charcot neuroarthropathy

In subjects with long standing DN, the bones of the foot may undergo osteoporotic changes and this may lead to the deformity of the foot. When extreme, the destruction and deformity leads to a grossly deformed foot called Charcot foot. In its acute phase,

the foot is red and swollen with elevated local temperature. The differentials of acute Charcot foot include acute cellulitis, osteomyelitis, acute gout and deep venous thrombosis. Untreated, it leads to recurrent micro fractures, bone resorption and development of irregular deformed foot, which is at high risk for foot ulceration (chronic Charcot foot). Sensorimotor neuropathy, autonomic neuropathy and an intact peripheral circulation constitute the prerequisites for development of Charcot neuroarthropathy. Management of acute Charcot foot includes offloading with a total contact cast (TCC), followed by the use of a brace (such as Charcot restraint orthotic walker (CROW), patellar tendon-bearing brace) to protect the foot. Bisphosphonates have been tried in acute Charcot foot, however long term efficacy in preventing foot ulceration and deformity is not known. Reconstructive surgery may be required to correct the deformities of chronic Charcot foot.

Differentiation from non-diabetic neuropathy

Like general population, patients with T1DM are also at a risk of developingnon-diabetic neuropathies. Some non-diabetic neuropathies like pressure palsies and chronic inflammatory demyelinating polyneuropathy are more common in patients with T1DM and T2DM. In a study of T2DM subjects, around 10% of patients with neuropathy had a non-diabetic etiology. Identification of non-diabetic neuropathies often provides an opportunity for specific treatment measures. Hence, it is often recommended to make a diagnosis of DN only after the exclusion of nondiabetic neuropathies. However, an extensive laboratory evaluation for non-diabetic neuropathies in all patients with diabetes and neuropathy may not be cost-effective. In a patient with diabetes, a combination of typical symptoms and symmetrical distal sensory loss or typical signs in the absence of symptoms is highly suggestive of DSPN and may not require additional evaluation or referral to a neurologist. In contrast, patients presenting with some atypical features mentioned below are more likely to have non-diabetic neuropathies and hence, should be evaluated for the same.

a) Onset of neuropathy at less than 5 years from the diagnosis of diabetes
b) Pure or predominant motor neuropathy
c) Asymmetrical neuropathy
d) Rapid onset or progression of neuropathy
e) Family history of non-diabetic neuropathy

Screening for diabetic neuropathy

Insensate feet are at a high risk for foot ulceration. Around 50% of T1DM patients with neuropathy may be asymptomatic. Hence, it is important to screen patients with T1DM at regular intervals for DN. It is surprising to know that DN is underdiagnosed not only by physicians but also by endocrinologists. Screening for DN should be initiated five years after the diagnosis of T1DM and repeated at least annually thereafter. Assessment should include a careful history and either temperature or pinprick sensation for small-fiber function and one or more of the following for large-fiber function: vibration sensation using a 128-Hz tuning fork, proprioception (joint position), light touch sensation using 10 g monofilament testing and ankle reflexes. The monofilament test uses 10g monofilament to assess light touch at the pressure points on the sole, and to detect large fiber neuropathy. The monofilament is placed at selected pressure points and just enough pressure is exerted for one second to buckle the filament. As per

the IDF recommendations, four sites should be tested-plantar surface of metatarsal head of first, third and fifth toe, and plantar surface of hallux. An abnormal response at any one site is diagnostic of Loss of Protective Sensation (LOPS). LOPS has been shown to be predict future foot ulcerations in various studies. Biothesiometry is a test that estimates the threshold of vibration in volts or microns using increasing levels of electrical stimulation. The threshold at which vibration is perceived is recorded, and if the patient can perceive vibration only above 15 V, the patient is said to have neuropathy. Nerve conduction studies should only be reserved for patients with atypical neuropathy. Special tests such as IENFD in skin biopsy, quantitative autonomic function testing and CCM should not be done routinely.

Cardiac autonomic neuropathy can be assessed by lack of heart rate variability on an ECG recording during 1-2 min deep breathing and demonstration of orthostatic hypotension (a fall in systolic or diastolic blood pressure by ≥ 20mm Hg or ≥ 10mm Hg, respectively, upon standing without an appropriate increase in heart rate). In a patient with erectile dysfunction, hypogonadism and thyroid dysfunction needs to be excluded (luteinizing hormone, total testosterone, prolactin, total T4 and thyroid stimulating hormone should be measured). The clinical tests and laboratory investigations to diagnose DN, and cardiac autonomic functions tests have been summarised in Table III and Table IV respectively.

Other investigations

Patients with suspected DN should be evaluated for glycemic control and other risk factors such as dyslipidemia. Common causes of non-diabetic neuropathies such as uremia, vitamin B12 deficiency, and hypothyroidism should be excluded. Although DN is a diagnosis of exclusion, it may not be cost-effective to extensively evaluate for other causes of non-diabetic neuropathies in all patients. An extended evaluation should be considered under the guidance of a neurologist in patients with atypical features as mentioned above.

Overview of management, referral and follow-up plan

Management involves achieving good and stable glycemic control, treatment of risk factors such as obesity, hypertension and dyslipidemia, and avoidance of smoking and alcohol use. Optimal glycemic control is the most effective therapy to reverse (in the initial stages) and prevent progression of neuropathy in T1DM. Maintaining glycated hemoglobin (HbA1C) level below 7% has been shown to reduce onset and progression of DN.

Despite a reasonable understanding of its pathophysiology, no pharmacological agent which can alter the natural history of neuropathic process has been found successful till date. We know that hyperglycemia leads to increased levels of markers of oxidative stress such as superoxide and peroxynitrite ions which lead to peripheral nerve damage. Besides, antioxidant defense mechanisms are also known to be impaired in patients with DN. Various therapies being tried/ under investigation for DN are aimed at reducing oxidative stress. These include aldose reductase inhibitors (epalrestat and zenarestat), antioxidants like α-lipoic acid, γ-linolenic acid and benfotiamine, and PKC inhibitor (ruboxistaurin)[12]. Of these agents, epalrestat, an aldose reductase inhibitor, which works by inhibiting glucose flux via polyol pathway, has shown some potential. In rat models with streptozotocin-induced diabetes and hyperglycemia induced peripheral neuropathy, epalrestat was found to reduce injuries to myelinated nerve fibers, non-myelinated nerve fibers and Schwann