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An Overview of Diabetic Neuropathy

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Author's contribution

The entire work of designing, writing, analyzing and managing the literature searches was done solely by me.

Review Article

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ABSTRACT

Purpose of Review: Diabetic Neuropathies are a heterogeneous by their symptoms, pattern of neurologic involvement, course, risk covariates, pathologic alterations, and underlying mechanisms that result into mono- and polyneuropathies, plexopathies and radiculopathies. It also ranges from subclinical functional impairment of cardiovascular reflexes and sudomotor functions to severe cardiovascular, gastrointestinal, or genitourinary dysfunction. Orthostatic hypotension, Resting tachycardia, and Heart Rate unresponsiveness to respiration are the hallmarks of Diabetic Autonomic Neuropathy. Diabetic Peripheral Neuropathy greatly affects all areas of a patient's life, including mood, sleep, self-worth, independence, ability to work, and interpersonal relationships. This review provides an overview of definition, etiopathogenesis, clinical assessment, diagnosis and management of the patients with Diabetic Neuropathies.

Summary and Results: Good clinical history and complete physical examination are the basis of assessment followed by therapeutic and laboratory studies. Strict glycemic control along with early detection and control of hyperlipidemia and hypertension, daily aspirin, smoking cessation and alcohol consumption in moderation may help to prevent, delay, or slow the progression of Diabetic Neuropathy. The main classes of agents used to treat Diabetic Peripheral Neuropathic pain include Tricyclic antidepressants, Anticonvulsants, Serotonin-Norepinephrine Reuptake Inhibitors, Opiates and Opiate-like substances, and topical medications. However, only two medications are approved specifically for the treatment of Diabetic Peripheral Neuropathic pain: Pregabalin and Duloxetine. Management must be individualized for each patient based on efficacy, side effects profiles and drug accessibility including cost.

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1. INTRODUCTION

Diabetes Mellitus represents a spectrum of metabolic disorders, which has been generating a huge global economic burden and has become a major health challenge worldwide [1]. According to International Diabetes Federation (IDF) 2012 update [2], the number of people with diabetes is increasing in every country with currently more than 371 million diabetics. Half of people with diabetes are undiagnosed or unaware about their disease. IDF has further updated that 4.8 million people died due to diabetes and more than 471 billion USD were spent on healthcare for diabetes. This morbidity and mortality of diabetes is due to development of both macrovascular and microvascular complications [3]. Macrovascular complications are common among diabetics, while, diabetes-specific microvascular complications (retinopathy, nephropathy, neuropathy) will eventually affect nearly all individuals with diabetes. Diabetic Neuropathy (DN) accounts for hospitalisation more frequently than other complications of diabetes and is also the most frequent cause among non-traumatic amputation and autonomic failure [4,5]. Diabetic Autonomic Neuropathy (DAN) accounts for silent myocardial infarction and shortens the lifespan by resulting in death in 25%– 50% of diabetic patients within 5–10 years of DAN [6]. This review summarizes key findings of definition, classification and risk factors of DN. Furthermore, it was designed to facilitate the clinician's understanding of DN by surveying etiopathogenesis, clinical assessment, current diagnostic and therapeutic approaches.

2. MATERIALS AND METHODS

A systematic review of MEDLINE, EMBASE, Wiley online and SAGE was undertaken using the MeSH terms regarding Diabetic Neuropathy. Terms combined with DN were classification, pathophysiology, epidemiology, diagnosis, and management options for DN. All of these articles were reviewed in their entirety. The inclusion criteria were primary literature of well-designed and controlled studies with clear results specific for DN.

3. RESULTS

3.1 Definition

Neuropathy is a common long term microvascular complication of Diabetes Mellitus type 1 and 2. Diabetic Neuropathies (DN) are a heterogeneous by their symptoms, pattern of neurologic involvement, course, risk covariates, pathologic alterations, and underlying mechanisms [7] that results into mono- and polyneuropathies, plexopathies and radiculopathies [8]. While, internationally agreed simple definition of Diabetic Peripheral Neuropathy (DPN) for clinical practice is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes mellitus after the exclusion of other causes" [9].

3.2 Classification

Table 1 represents classification of neuropathies observed in diabetes based on a modification of the classifications proposed by Dyck et al. [10,11] and Vinik et al. [12,13].

Table 1. Classification of diabetic neuropathies

Generalised	Focal and multifocal	Autonomic	Miscellaneous
Typical: Distal Symmetric Polyneuropathy ➢ Acute Sensory ➢ Chronic Sensorimotor • Small fibre neuropathies • Large fibre neuropathies	***Compression*** ➢ Median: Carpal tunnel ➢ Ulnar: Cubital tunnel ➢ Fibular: Fibular head ➢ Lateral Femoral Cutaneous: Inguinal ligament	➢ Cardiovascular Autonomic Neuropathy ➢ Gastrointestinal Autonomic Neuropathy ➢ Genitourinary Autonomic Neuropathy ➢ Hypoglycemic Unawareness & Associated Autonomic Failure ➢ Sudomotor Autonomic Neuropathy	➢ Mixed ➢ Polyneuropathy after ketoacidosis ➢ Polyneuropathy with glucose impairment ➢ Neuropathy with weight loss "Diabetic Cachexia"
Atypical ➢ Insulin Neuritis/ Treatment Neuropathy ➢ Chronic Inflammatory Demyelinating Polyneuropathy(CIDP) ➢ Mononeuritis Multiplex ➢ Diabetic Amyotrophy	***Ischemic*** ➢ Cranial Nerve palsy(3,6,7) ➢ Focal Limb Neuropathies ➢ Cervical Radiculoplexus Neuropathies ➢ Thoracolumbar Radiculoneuropathy ➢ Lumbosacral Radiculoplexus Neuropathies		

3.3 Epidemiology

3.3.1 Prevalence

Estimates of prevalence of DN vary widely from 5% to nearly 60% and sometimes 100% if patients with asymptomatic abnormalities of nerve conduction are included [14]. A case control study conducted by Booya *et al* has found neuropathy in 10% of diabetic patients at the time of diagnosis and overall in 50% of patients with a 25-year history of the disease [15]. Epidemiological data indicates that the prevalence of Diabetic Peripheral Neuropathy is higher in type 2 than type 1 diabetes; where, in a study proposed by Kastenbauer *et al* had observed an evidence of Peripheral Neuropathy in nearly one third of patients with type 1 diabetes and more than half of patients with type 2 diabetes [16]. However, another population-based cohort studies have shown that 66% of type I and 59% of type 2 diabetics had objective evidence of Diabetic Peripheral Neuropathy [17]. In the US, the prevalence of painful Diabetic Neuropathy has been estimated among 20–24% of diabetic patients with Peripheral Neuropathy [18]. In a recent MONICA/KORA survey from Augsburg, Germany, the prevalence of painful polyneuropathy was found to be 13.3% in diabetic subjects, 8.7% in individuals with impaired glucose tolerance, 4.2% in individuals with impaired fasting glucose, and 1.2% in individuals with normal glucose tolerance [19]. While, studies

conducted in the Middle East Region (MER) report higher rates of painful Diabetic Peripheral Neuropathy (DPN), ranging from 35% to 65% [20,21]. 50% of diabetic patients with polyneuropathy have asymptomatic Cardiac Autonomic Neuropathy, while 100% of patients with symptomatic Cardiac Autonomic Neuropathy have polyneuropathy [22,23].

3.3.2 Risk factors

The European Diabetes Complications Prospective Study (EURODIAB), involving 1,101 patients with type 1 diabetes followed for a mean of 7.3 years has concluded smoking, glycosylated haemoglobin (HbA1C), diabetes duration, and components of the metabolic syndrome (including hypertension, obesity, triglycerides and cholesterol) were all associated with an increased risk of polyneuropathy [24]. Duration of diabetes, age, long term poor glycemic control, high blood pressure, high triglycerides levels, low HDL, high HbA1C, peripheral arterial disease, high alcohol intake, increased height, smoking, obesity, retinopathy, renal failure, low socioeconomic status, co-morbid diseases, missed doses of Hypoglycaemic agents > 5 times/month, treatment with insulin are the various factors studied and proved that raises the likelihood of neuropathy [15,24,25,26,27,28,29]. There are findings that have suggested that neuropathy can develop, despite intensive control of the glucose level [24]. However, it has been suggested that consumption of Oral Hypoglycemic Agents such as Glyburide and Angiotensin Converting Enzyme Inhibitors (ACEI) inhibit the progression of neuropathy irrespective of blood glucose level [30]. But studies have recommended to further elaborate the effects of ACEI and Oral Hypoglycaemic Agents on neuropathy using a randomized clinical trial [15].

3.4 Etiopathogenesis

The precise pathogenesis of diabetic peripheral neuropathy despite recent advances remains obscure; however, consensus is that neuropathy in diabetes mellitus is a multifactorial disease. The diabetic state produces impaired neurotropism, axonal transport and gene expression through at least four major pathways. 1) Excess glucose is diverted away from glycolysis by the polyol pathway that depletes NADPH and cellular antioxidant capacity. 2) Glucose also may become oxidized and form AGEs that alter extracellular matrix, activate receptors that produce ROS intermediates, and alter intracellular protein function. 3) PKC becomes activated either directly by glycolytic intermediates or indirectly as a second messenger for stress hormones, leading to increased vascular disease, inflammation, and oxidative stress. 4) Partial glycolysis causes accumulation of glycolytic intermediates and leads to escape of fructose-6-phosphate along the hexosamine pathway that increases vascular disease and further ROS generation [31]. Other metabolic factors includes altered fatty acid metabolism with depletion of prostagladin precursors especially linolenic acid and PGE1 which play a major role in regulating tissue Na^+-K^+ ATPase activity, and reduced concentration of nerve growth factors [32]. However, Tesfaye *et al* [33] have demonstrated vascular endoneurial hypoxia resulting from arteriovenous shunting among epineural vessels with the proliferation of new leaky neural vessels among diabetic patients.

Thus, Metabolic abnormalities, Microvascular insufficiency, Auto-immune processes and deficiencies of Neurotropism results in the complex mechanisms leading to damage, dysfunction and finally Diabetic Neuropathy [Fig. 1].

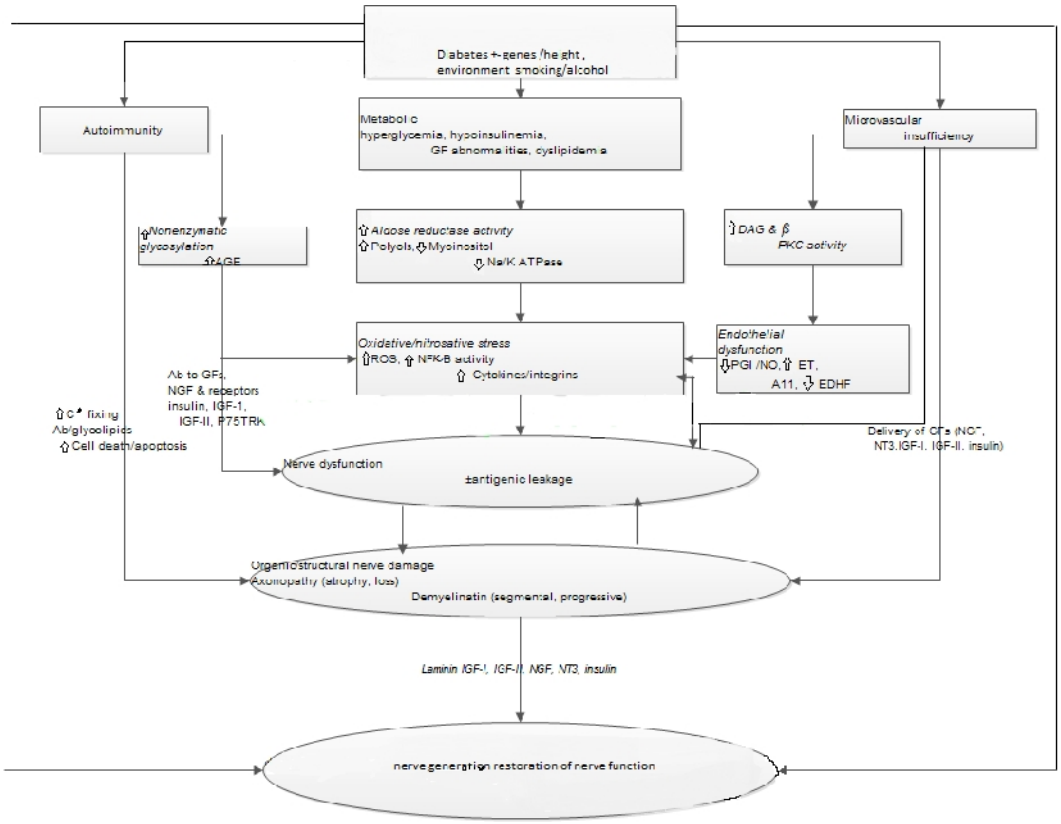

Fig. 1. Pathogenesis of diabetic neuropathies [34]

[Ab, Antibody; AGE, advanced glycation end-product; ATPase, adenosine triphosphatase; DAG, diacylglycerol; EDHF, endothelial-derived hyperpolarizing factor; ET, endothelin; GF, growth factor; IGF, insulin-like growth factor; K, potassium; Na, sodium; NFkB, nuclear factor kappa B; NGF, nerve growth factor; NO, nitric oxide; NT3, neurotropin 3; PGI, prostaglandin I; PKC, protein kinase C; ROS, reactive oxygen species].

Unfortunately, the basic research in DN has been focused on carbohydrate metabolism; whereas amino acids, electrolytes, and lipid biochemical changes, which are also associated with DM, have not been investigated with the same vigour.

3.5 Clinical Characteristics

3.5.1 Distal symmetric polyneuropathy

3.5.1.1 Acute sensory neuropathy

Acute sensory neuropathy is rare but tends to follow the periods of poor metabolic control (e.g., ketoacidosis), a sudden change in glycemic control [35], (e.g., “insulin neuritis”), or “diabetic cachexia” which has been reported in diabetes associated with weight loss, depression and eating disorder [36]. It is characterized by the acute or subacute onset of severe sensory symptoms (as detailed below) with marked nocturnal exacerbation and weight loss but few neurologic signs on examination of the limbs. It is self limiting and

invariably responds to simple symptomatic treatment with establishment of stable glycemic control.

3.5.1.2 Chronic sensorimotor DPN

A distal sensory neuropathy with an insidious onset is the most common neuropathy in patients with diabetes [17]. It is a length-dependent process, with the most distal portions of the longest nerves affected earliest, resulting in a glove-stocking distribution before progressing proximally [37]. Thus, the earliest symptoms typically involve the toes, and then ascend. Hand symptoms can occur when DPN progresses to include the hands in a length dependent process, but more commonly occur because of coexisting compression neuropathies in the hands [38,39]. If there is upper limb sensory loss in a glove distribution, the level of impairment in the legs has to have reached mid thigh. If not, look for another explanation for the upper limb sensory loss. Small fibre damage affects sensation of temperature, light touch, pinprick, and pain. While, large fibre damage diminishes vibratory sensation, position sense, muscle strength, sharp-dull discrimination, and two-point discrimination. Inaugural symptoms of Length Dependent Diabetic Polyneuropathy (LDDP) include numbness, burning feet, pinsand-needles sensations and lightning or burning pain which can be exacerbated by contact. The symptoms are often most pronounced when tired or stressed [40] and at night with bed clothes irritating hyperaesthetic skin [41]. The sensory neuropathy can be totally silent and detected only by systematic neurological examination of the feet, or can be revealed by painless trauma or burns, or by trophic changes that include plantar ulcers or neuropathic osteoarthropathies (Charcot's joints).When evaluating for sensorimotor neuropathy, it is important to ask the patient about recent falls and to look for loss of Achilles and patellar tendon reflexes, gait ataxia, and balance problems. DPN greatly affects all areas of a patient's life, including mood, sleep, self-worth, independence, ability to work, and interpersonal relationships [41,42].

3.5.2 Focal and Multifocal neuropathy

3.5.2.1 Cranial nerve palsy

Cranial neuropathy of III, IV, and VI, as well as Bell's palsy in patients with diabetes occurs due to a microvascular "infarct," which, in the majority, resolves spontaneously over several months. Third (3.3%) and sixth (3.3%) cranial nerve palsies seem to be equal and greater in prevalence than fourth (2.1%) nerve palsy [43]. Cranial nerve III involvement results in ophthalmoplegia, ptosis, and diplopia with sparing of pupillary function [44]. In patients with third nerve palsy, it is advisable to perform a brain MRI scan and a Magnetic Resonance Angiogram to exclude other causes of Oculomotor Nerve palsy. Patients with diabetic Oculomotor Nerve palsy recover spontaneously within 2–3 months, although relapses on the opposite side of the body can occur. Multiple cranial nerve palsies are extremely rare.

3.5.2.2 Entrapment neuropathy

Upto one third of patients with diabetes may have a nerve entrapment. Common nerves involved are the ulnar, median, peroneal, and medial plantar nerves. Electrophysiological studies are the most helpful in identifying blocks in conduction at the entrapment sites. However, entrapments may require decompression, but initial management should be expectant with strong reassurance to the patient for recovery [45].

3.5.2.3 Diabetic truncal radiculoneuropathy

It involves pain over a focal area on the chest and/or abdomen, which is usually unilateral [46], often burning in quality, and in a variety of distributions reflects a nerve root or intercostal nerve trunk involvement. Focal contact hyperesthesia may be seen in the same area and further, focal anterior abdominal wall weakness may also be evident. Associated weight loss in some cases may be profound. However, good prognosis with spontaneous recovery over several months has been reported.

3.5.2.4 Lumbosacral radiculoplexus neuropathy (Bruns-garland syndrome)

It is most common in older patients with type 2 DM and is rarely encountered in those with type 1 DM. Males are more frequently affected than females. Severe burning and aching pain which is worse at night affects lower back, buttocks or anterior thighs. Weakness follows pain within a matter of a few days to several weeks and usually unilateral at onset. Later may be bilateral but always asymmetrical in nature. It mainly involves proximal muscles, but not uncommon for distal group to be involved. It may slowly progress over several weeks. Weight loss may be dramatic (>10–20 kg). Recovery is heralded by stabilisation of body weight and resolution of pain with reasonable prognosis. Muscle strength improves slowly over many months, but a number of patients never regain normal lower limb strength.

3.5.3 Autonomic neuropathy

Diabetic Autonomic Neuropathy (DAN) affects the sympathetic, parasympathetic and enteric nerves of various organs of the body. Although Autonomic Neuropathy may occur at any stage of diabetes, [47,48] usually it develops in patients who have had the disease for 20 years or more with poor glycemic control. It ranges from subclinical functional impairment of cardiovascular reflexes and sudomotor functions to severe cardiovascular, gastrointestinal, or genitourinary dysfunction (Table 2). Orthostatic hypotension, Resting tachycardia, and Heart Rate unresponsiveness to respiration are hallmark of Diabetic Autonomic Neuropathy. Many investigators have considered Autonomic Neuropathies to be irreversible. However, cardiac sympathetic dysinnervation has been shown to regress with tight glycemic control [49] but it is considered as a most life threatening and carries a higher risk of mortality [50,51].

Table 2. Signs and symptoms of various diabetic autonomic neuropathy

Type of Autonomic Neuropathy	Signs and Symptoms
Cardiovascular	Exercise intolerance, fatigue, resting tachycardia, syncope, dizziness, lightheadedness, balance problems, orthostatic hypotension, painless myocardial infarction, sudden death [51,52,53,54].
Gastrointestinal	Dysphagia, bloating, nausea and vomiting, diarrhea, constipation, loss of bowel control, faecal incontinence [51,55].
Genitourinary	Loss of bladder control, urinary tract infection, urinary frequency or dribbling, dysuria, urgency, nocturia, erectile dysfunction, loss of libido, dyspareunia, vaginal dryness, anorgasmia [56,57].
Sudomotor	Gustatory sweating, pruritus, dry skin, limb hair loss, calluses, reddened areas, nail dystrophies, hyperhidrosis and heat intolerance in the upper torso or anhidrosis in the lower extremities, foot ulcers and edema [56].
Endocrine	Hypoglycemic unawareness [58].
Pupillary	Miosis, disturbances of dilatation, Argyll Robertson pupil.
Miscellaneous	Difficulty driving at night, depression, anxiety, sleep disorders, cognitive changes.

3.5.4 Neuropathy and impaired glucose tolerance

There have been a number of series suggesting than more than 50% of the patients referred to neuromuscular clinics with a diagnosis of “Idiopathic” painful sensory neuropathy have abnormal glucose metabolism [59]. Furthermore, there is increasing evidence that patient with milder degrees of abnormal glucose metabolism, including Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (formerly referred to as “borderline” diabetes), are also at risk for developing symptomatic polyneuropathy [60]. The neuropathy associated with IGT is clinically similar to early diabetic neuropathy, with preferential injury to small nerve fibres resulting in pain and autonomic dysfunction [61]. However, Sumner *et al* [62] has concluded that neuropathy associated with IGT is milder than the neuropathy associated with DM where IGT had predominantly small fibre neuropathy, compared to patients with DM, who had more involvement of large nerve fibres. Patients presenting with unexplained painful sensory neuropathy should be evaluated for impaired glucose metabolism with a 2-hour Oral Glucose Tolerance Test (OGTT). The diagnostic evaluation often reveals normal nerve conduction studies, and diagnostic confirmation requires use of validated measures of small fibre function, most frequently skin biopsy with assessment of intraepidermal nerve fibre density, which is abnormal in the majority of patients [63]. Patients with abnormal OGTT should be referred for lifestyle interventions and/or initiation of oral hypoglycemic agents in addition to management of neuropathy symptoms.

3.6 Diagnostic Assessment

Good clinical history and complete physical examination are the basis of assessment. A detailed history includes documentation of symptoms of DPN and review of diabetes history, disease management, daily glycemic records, and previous hemoglobin A1C levels. Asking about similar symptoms in family members may help in distinguishing familial neuropathies. Medication history including use of over-the counter products and herbal or homeopathic

products and environmental exposures should be assessed. A careful history also includes differential diagnosis (Table 3) because diabetes is not the one on the list of causes of peripheral neuropathy [64,65].

Table 3. Differential diagnosis of diabetic neuropathies

Types	Syndromes
Congenital/Familial	Charcot-Marie-Tooth Syndrome
Traumatic	Entrapment Syndromes
Inflammatory/Infiltrative	Sarcoidosis, Leprosy, Lyme disease, HIV, Refsum's disease, Amyloidosis, Periarteritis Nodosa
Neoplastic	Carcinoma, Paraneoplastic syndrome, Myeloma, Leukemias, Lymphomas
Metabolic/Endocrine	Diabetes, Uremia, Pernicious Anemia, Hypothyroidism, Acute Intermittent Porphyria
Vascular	Diabetes, Vasculitis
Toxic	Alcohol, Heavy Metals (Lead, Mercury, Arsenic), Hydrocarbons, Drugs (Pyridoxine toxicity), Chemotherapeutics.
Autoimmune	Diabetes, Phospholipid Antibody Syndrome, Guillain-Barré Syndrome, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multifocal Motor Neuropathy.

A complete physical examination with shoes and socks removed should be done to screen and assess vibration perception (using a 128-Hz tuning fork), light touch (cotton wisp), pressure (10-g monofilament), superficial pain (sterile safety pin), temperature sensation, ankle reflexes and joint proprioception test. A 10-g filament, which is widely available, disposable, and easy to use, is very useful in assessing protective sensation at the distal halluces and identifying the risk of foot ulceration [37,66]. Its sensitivity alone ranges from 20% to 64% [67,68] and likely improves if multiple sites on the foot are tested (8 sites recommended). Combinations of more than one test have nearly 87% sensitivity in detecting DPN. Weakness of small foot muscles (extensor hallucis longus and extensor digitorum brevis) should be assessed. Peripheral pulses, resting pulse and blood pressure on lying and standing should be measured. The feet should be examined for ulcers, calluses, and deformities, and footwear should be inspected. Indeed, longitudinal studies have shown that a simple clinical examination is a good predictor of future foot ulcer risk [69].

Therapeutic and Laboratory studies should be ordered as dictated by clinical findings and might typically include a complete blood count, general chemistries, HbA1c levels, serum B12, thyroid function, blood urea nitrogen, serum creatinine, antinuclear antibodies, sedimentation rate, rheumatoid factor, and urine protein electrophoresis. Nerve-conduction studies evaluate whether the myelin or nerve axon is affected and helps to pinpoint a specific diagnosis. It demonstrates slowing of conduction velocity across the compressed segment (ulnar, fibular, tibial nerve) or increased distal latency compared to nearby nerves (median nerve) in compression mononeuropathies. Electromyography can distinguish if weakness is from a nerve or muscle disorder. Nerve biopsy is reserved for patients with severe and progressive disease and can helps to identify vasculitis, amyloidosis, sarcoidosis, and several types of hereditary neuropathies. After thorough evaluation, treatment is geared to the underlying etiology.

Assessment of cardiovascular autonomic nervous system function can be done by measuring heart rate variability, the heart rate response in postural change from lying or

sitting to standing, the blood pressure change from lying or sitting to standing, and the diastolic blood pressure response to a sustained hand grip. Heart rate variability can be assessed by measuring the heart rate response to paced deep breathing, the Valsalva maneuver, and spectral analysis. The heart rate response to deep breathing and the heart rate response to a change in posture to the standing position predominately reflect parasympathetic function [51]. The heart rate response to the Valsalva maneuver reflects both parasympathetic and sympathetic function fairly equally [51]. However, a Valsalva maneuver must not be performed in patients with proliferative retinopathy. The change in blood pressure from a lying or sitting position to a standing position and the blood pressure response to a sustained hand grip reflects sympathetic nervous system function [51]. Stress testing should be considered, before any patient with diabetes, starts with an exercise program [70].

Assessment of autonomic neuropathy affecting the gastrointestinal tract can be done by endoscopy and scintographic measurement of esophageal bolus transit time for esophageal dysfunction; scintography, isotope breath tests, and ultrasonography for gastroparesis; hydrogen breath test for diabetic diarrhea; barium enema for constipation; and digital examination of the rectum, anorectal manometry, endoanal ultrasonography, colon transit tests, proctoscopy and sigmoidoscopy for fecal incontinence [51,71].

A complete work-up for impotence in men should include comprehensive history (sexual, medical, drug use, risk factor assessment and psychosocial factors) [72]; hormone levels; measurement of nocturnal penile tumescence; tests to assess penile, pelvic, and spinal nerve function; cardiovascular autonomic function tests; and measurement of penile and brachial blood pressure. The use of drugs associated with erectile dysfunction which includes tranquillizers, antidepressants (tricyclics, selective serotonin reuptake inhibitors) and antihypertensives (ß-blockers, vasodilators, central sympathomimetics, ganglion blockers, diuretics, ACE inhibitors) should be reviewed.

The diagnosis of diabetic neurogenic bladder dysfunction is made most readily with complete urodynamic testing. This may include renal function test, cystometry, uroflow, simultaneous pressure/flow studies, sphincter electromyography and urethral pressure profilometry or evaluation of leak-point pressures. Cystometric and Urodynamic studies are the confirmatory tests [51]. Postvoid residual volume (PVR) and urine dipstick (optional culture) should be performed yearly in all patients with insulin dependent diabetes [73].

Assessment of sudomotor function can be done with the Quantitative Sudomotor Axon Reflex Test (QSART) [61, 74], Thermoregulatory Sweat Test [74], Sympathetic Skin Response [75] or Neuropad/ Indicator Plaster method [76] or Quantitative Direct and Indirect Reflex Test (QDIRT) [77].

3.7 Management

3.7.1 Prevention

Strict glycemic control is perhaps the single greatest prevention measure for neuropathy [78]. The American Association of Clinical Endocrinologists recommends an A1C value of less than 6.5 percent in diabetic patients [79]. Early detection and control of hyperlipidemia and hypertension, daily aspirin, smoking cessation and alcohol consumption in moderation may help to prevent, delay, or slow the progression of diabetic neuropathy [80].

3.7.2 Screening

All patients with diabetes should be screened for Diabetes Neuropathy at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. If screening is negative, this should be repeated annually; if positive, appropriate diagnostic tests and symptomatic treatments should be instituted [81].

3.7.3 Foot care

Physician should examine the patient's feet visually at each visit to detect evidence of neuropathy or early lesions and educate regarding preventive measures and provide referral to a podiatrist as necessary. Patients should be instructed to inspect their feet daily for dry or cracking skin, fissures, plantar callus formation, and signs of infection between the toes and around the toenails [82]. Patients should be encouraged to use proper footwear and avoid sources of possible trauma, such as walking barefoot, cutting nails incorrectly, and exposing their feet to hot objects or chemicals. The off-loading capacity of footwear using orthotic inserts may be helpful in stabilizing the feet and preventing pressure related diabetic foot ulcer [83]. The American Diabetes Association (ADA) [84] recommends a thorough annual foot examination by a health care professional for all patients with diabetes.

3.7.4 Treatment

The first step in the management of DPN is tight glycemic control and correction of any associated other metabolic derangements. In the Diabetes Control and Complications Trial (DCCT), strict glycemic control not only decreased the incidence of neuropathy but also slowed its progression by 57% [78].

3.7.4.1 Diabetic peripheral neuropathy

The ideal therapy should be directed at preventing or arresting the progressive loss of nerve function and improving symptoms with minimal side effects. However, once pain develops, current treatment options are not specific for the underlying cause of nerve damage and are aimed often only at partially alleviating the symptoms due to significant adverse effects. Evidence-based treatment guidelines in Western countries [85,86] and in the MER [87] consistently recommended Pregabalin and Gabapentin as first-line treatments for painful DPN, with Duloxetine as a second-line treatment. However, various evidences support the use of Tricyclic Antidepressants [88] as the first-line treatment unless there are contraindications. Because patients often have multiple comorbidities, physicians must consider potential adverse effects and possible drug interactions before prescribing a medication. Thus, treatment must be individualized for each patient based on efficacy, side effects profiles and drug accessibility including cost.

- Tricyclics Antidepressants (TCA): Amitriptyline and Imipramine has been confirmed in several randomized controlled trials [66,88,89]. An updated Cochrane review of Antidepressants for treating neuropathic pain revealed an overall effectiveness, with a Number Needed to Treat (NNT) of 1.3 for diabetic neuropathy based on five studies involving TCAs [90]. Although TCAs are generally affordable and effective, but one in five patients discontinues therapy because of adverse effects [90]. Physicians should be cautious when prescribing them for patients with narrow-angle glaucoma, epilepsy, benign prostatic hypertrophy, orthostasis, urinary retention, impaired liver function, or thyroid disease due to anticholinergic effects of TCAs.

QTc interval should be initially assessed in those with additional risk factors of syncope or presyncope, cardiovascular disease, electrolyte disturbance, and older age (>60yrs) [90,91]. If QT prolongation is present, other medications should be used because of the risk of torsades de pointes.

- Serotonin-norepinephrine reuptake inhibitors (SNRIs) and Selective serotonin reuptake inhibitors (SSRIs): SNRIs (Venlafaxine and Duloxetine) are a promising category of antidepressants for treatment of Diabetic Peripheral Neuropathic pain. They are better tolerated and have fewer drug interactions than TCAs. A 2007 Cochrane review examined three studies of Venlafaxine for neuropathic pain, revealing a NNT of 3.1 [90]. A 2006 Randomized Controlled Trial (RCT) revealed a NNT of 5.1 with the use of Duloxetine 60 mg once per day and twice per day [92]. While, SSRIs (Citalopram and Paroxetine) have also been used to treat Diabetic Peripheral Neuropathic pain; however, there is only limited evidence showing a beneficial role and in addition, SSRIs are considered less efficacious than SNRIs [93]. However, patients on Duloxetine therapy should have their blood pressure, heart rate, and liver enzymes monitored.
- Anticonvulsants: Gabapentin and Pregabalin are recently confirmed in RCT as first-line treatment for Diabetic Peripheral Neuropathic pain [85,86,87]. They are alpha2-delta inhibitors which act on the dorsal horn of the spinal cord to inhibit voltage gated calcium channels. A 2005 Cochrane review evaluating the use of Gabapentin in painful neuropathy calculated a combined NNT of 4.3 from five studies of DPN pain and two studies of postherpetic neuralgia and mixed neuralgia [94]. Pregabalin is the second agent approved by the FDA for the indication of PDN, while, Duloxetine being the first approved agent. Pregabalin has been evaluated in three parallel, placebo-controlled studies in the treatment of PDN with the results of NNT of 4.2 [95,96,97,98]. The advantage of Gabapentin and Pregabalin is their renal excretion and lack of interaction with other medications. Pregabalin is effective when given twice daily, in contrast to Gabapentin, which is usually given in three daily doses. Main side effects include drowsiness, dizziness, peripheral oedema, weight gain, and myoclonic jerks at higher doses.
- Other agents: N-methyl-D-aspartate (NMDA) antagonists **(**Dextromethorphan, Memantine, Amantadine), Opioids (Morphine Sulfate, Tramadol, Oxycodone), Antioxidant (alpha Lipoic Acid), Anti-Arrhythmic agents (Mexiletine), Capsaicin cream/patch and Isosorbide Dinitrate spray are other options for the treatment of DPN.
- Combination therapy: If combination therapy is necessary, physicians should consider the mechanism of action when choosing medications and consider consulting a pain management specialist or neurologist [99]. It is important to avoid combining TCAs with SSRIs or SNRIs to avoid Serotonin Syndrome, a life-threatening condition with autonomic and neurologic symptoms [100]. Combination therapy with Opiates can be considered [101], where, one study showed a decreased need for Opiates when combined with Gabapentin [102].

3.7.4.2 Autonomic neuropathy

Antioxidants and Cardioselective Beta-blockers may be beneficial in Cardiac Autonomic Neuropathy [48]. Management of Orthostatic Hypotension consists of educating the patient regarding strategies to avoid or address reversible causes of hypotension by raising the head end of the bed, increasing salt intake to 10–20 g/day, small frequent meals, two cups of strong coffee, increased fluid intake, wearing clothing such as compression/elastic stockings that increase venous return, Fludrocortisone 200 mg or Ibuprofen 400 mg thrice

daily (better tolerated than Indomethacin) or Sympathomimetic agents [51,56]. Proton Pump therapy is conventionally used for patients with Esophageal dysmotility [57]. Fluid consumption immediately after consumption of medications should be advised in order to avoid pill-induced esophagitis in these patients [57]. Diets low in fat and soluble fiber may be beneficial in patients with gastroparesis [51,57], although pharmacotherapy with Prokinetic agents (Metoclopramide, Erythromycin and Domperidone) is the mainstay of therapy [57]. Domperidone may now be regarded as the current 'first-line' agent owing to adverse effects with Metoclopramide and Erythromycin. The management of diarrhoea, constipation and faecal incontinence is still largely symptomatic once specific other causes like Celiac disease and Exocrine Pancreatic Insufficiency are excluded [103]. Management of Erectile dysfunction should include Psychological Counseling; however, pharmacotherapy with the PDE5 inhibitors (Sildenafil, Vardenafil, Tadalafil) is the mainstay of therapy [51,57] provided there is no contraindication to its use. Treatment of bladder dysfunction may be behavioural (bladder retraining, pelvic floor exercises and fluid intake schedule), pharmacological (antimuscarinic agents, cholinergic agents, tricyclic antidepressants, alpha adrenergic agonists and Baclofen), or surgical (selective pudendal nerve block) [104,105]. Treatment of choice for neurogenic bladder dysfunction with partial or complete urinary retention or acontractile bladder remains clean intermittent catheterization [106].

4. CONCLUSION

Diabetic neuropathy is a debilitating disorder affecting around 50% of all diabetic people and results in functionality, mood, and sleep disturbances. It can also cause sensorimotor deficits, silent cardiac ischemia, orthostatic hypotension, vasomotor instability, hyperhidrosis, gastroparesis, bladder dysfunction, and sexual dysfunction. All diabetic patients, regardless of their type of diabetes, duration of diabetes, or age, require careful clinical examination of the lower extremities and feet at least once a year. The minimum requirements for diagnosis of painful peripheral neuropathy are history and assessment of symptoms by simple questionnaire, along with complete neurological examination.

Treatment should encompass relief of pain, as well as improvement in quality of life. Maintenance of aggressive control of blood glucose, HbA1c, blood pressure, and lipids with annual screening exam, pharmacological therapy and/or lifestyle changes are the keys to prevent and delay the complications of diabetes and diabetic neuropathy. Treatment must address the risk of falls, (hip) fractures and other injuries in patients with large fibre neuropathy, poor proprioception and ataxia, as well as those with orthostatic hypotension and autonomic neuropathy. This involves prevention and treatment of osteoporosis, patient and caregiver education, emphasis on gait training and use of ambulatory aids. Intensive foot ulcer prevention and treatment is mandatory. Chronic pain, disability and insomnia almost invariably lead to depression, which must be sought out and treated. Management requires excellent communication between patient and provider for diagnosis, decisions about which medication to start, expectations of a medication's effectiveness, monitoring for adverse events, and adherence to the medication plan to prevent relapse of symptoms.

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CONFLICT OF INTEREST

Author has declared that no conflicting interests exist.

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