A MINI-REVIEW ON DIABETIC NEUROPATHY

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ABSTRACT: ***The global epidemics of prediabetes and diabetes have resulted in a commensurate epidemic of these conditions' consequences. The most common complication is neuropathy, among which distal symmetric polyneuropathy (referred to as diabetic neuropathy in this Primer) is particularly common. Diabetic neuropathy is a loss of sensory function in the lower limbs that begins distally and is accompanied by pain and significant morbidity. Diabetic neuropathy affects at least half of people with diabetes throughout time.***
In individuals with type 1 diabetes, glucose management significantly slows the evolution of diabetic neuropathy, while the effects are less dramatic in those with type 2 diabetes. These discoveries have prompted additional research into the aetiology of diabetic neuropathy, as well as new 2017 recommendations for preventing and treating the illness that are tailored to each type of diabetes. New guidelines for the management of painful diabetic neuropathy using several types of medicines have also been released, with an emphasis on avoiding the use of opioids. Despite significant progress in our understanding of the intricacies of diabetic neuropathy over the last decade, the processes driving neuropathy in type 1 and type 2 diabetes remain unexplained. Future discoveries on disease pathogenesis will be crucial to successfully address all aspects of diabetic neuropathy, from prevention to treatment.
Keywords: Diabetes mellitus, Diabetic neuropathy, Neuropathic pain, Peripheral neuropathy.

I. INTRODUCTION

Diabetes mellitus is a group of metabolic illnesses in which a person has excessive blood glucose as a result of the body failing to create enough insulin or failing to react to the insulin that is produced. Polyuria (frequent urine), polydipsia (expanded thirst), polyphagia (expanded appetite), and a negative nitrogen balance are all indicators of excessive hyperglycemia, which is the main life threat of our day.[1] It is a collection of hormonal and metabolic disorders characterized by hyperglycemia and glycosuria, as well as disruptions in sugar, fat, and protein metabolism due to flaws in insulin secretion, activity, or both.

Diabetic people are becoming more common all over the world on a daily basis. After cardiovascular disease and cancer, diabetes is the third most common and dangerous disease. According to the International Diabetes Federation, the estimated global incidence of diabetes mellitus in 2010 is 239 million people. According to the International Diabetes Federation (2011), the number of diabetics is expected to rise from 366 million in 2011 to 552 million by 2030. With more diabetic patients than any other country, India is at the top of the list. The absolute number of people living with diabetes in India is estimated to be around 50.8 million in 2010, rising to 87.0 million by 2030. [2] Glucose is a simple sugar contained in food and a vital supplement that acts as a primary source of energy for the body's cells to function properly. Sugars are broken down in the small intestine and absorbed into the circulatory system by intestinal cells, where they are delivered to all of the body's cells. Because glucose cannot enter the cells on its own, it requires insulin to do so. Despite the existence of abundant glucose in the circulatory system, the cells starve for energy in the absence or absence of insulin. In some types of diabetes, the failure of cells to utilize glucose results in an unanticipated situation of famine, despite the presence of a large amount of unutilized glucose that is inefficiently excreted in the urine.

If not treated early enough, it can cause irreversible damage or consequences such as neuropathy, retinopathy, nephropathy, vascular damage, erectile dysfunction, non-alcoholic fatty liver disease, and many more. [3,4,5,6,7,8,9,10,11,12,13,14,15]

II. DIABETIC NEUROPATHY

Diabetic neuropathic syndromes are a common consequence of the disease. Chronic diabetic peripheral sensorimotor neuropathy (DPN) is by far the most common, affecting up to 50% of diabetics[9,10]. DPN is linked to an increased risk of death and morbidity, owing to its two main clinical manifestations, diabetic foot ulceration

and neuropathic pain[11–13]. Diabetic foot ulcers are caused by a complicated interplay of risk factors and patient behaviors, although sensory loss as a result of DPN is the most common cause. [14] Lower-limb complications of diabetes are costly and a significant burden for patients, with potentially fatal consequences such as amputation and death. [11,12,14] In addition, up to 50% of DPN patients experience severe neuropathic symptoms (painful-DPN).[15]These painful symptoms are commonly severe and often lead to depression, anxiety, and sleep disorders, and reduced quality of life. [16,17]

Neuropathy is a type of nerve damage that begins with the longest nerves in the toes and advances proximally. Numbness, tingling, discomfort, and/or weakness in the distal lower extremities are common symptoms. Although diabetes is well recognized as the most important metabolic risk factor for neuropathy, treating hyperglycemia alone is insufficient to prevent neuropathy in those with type 2 diabetes[18]. In those with type 2 diabetes, neuropathy affects 8–45% of people, with around a quarter of individuals reporting pain[19]. Diabetic neuropathy (DN) is a significant and prevalent type 1 and type 2 diabetic condition. It's a sort of nerve injury-induced by high blood sugar levels for an extended period of time. The illness normally takes a long time to develop, possibly several decades.

III. EPIDEMIOLOGY OF DN

Diabetic neuropathy is a common illness that has a significant impact on patients by increasing their risk of falling, causing discomfort, and lowering their quality of life (QOL)20. Diabetic neuropathy and its complications cost the United States more than $10 billion per year[21]. Several studies have looked at the prevalence and/or incidence of neuropathy, albeit each study's definition of neuropathy differs. Neuropathy was found to be prevalent in 1%–4% of people in two population-based investigations utilizing door-to-door screening, with diabetes accounting for 40–55 percent of cases [22,23]. Similarly, after a diagnostic workup by a neurologist, almost half of instances of neuropathy were ascribed to diabetes in another study[24].

Individuals with T2DM have a higher rate of neuropathy (6,100 per 100,000 person-years) than those with T1DM (2,800 per 100,000 person-years) [25,26,27]. Neuropathy is more common in people with T2DM (8–51 percent) [28,29,30] than in those with T1DM (11–50 percent). [30,31,32]. Importantly, when silent neuropathy is considered, the prevalence rises even more, with 45 percent of T2DM patients and 54 percent of T1DM patients acquiring neuropathy[30]. The increased prevalence of neuropathy in T2DM patients, compared to T1DM patients, is likely due to a combination of factors, including differences in the age of onset of diabetes and changes in the underlying pathophysiology.

Diabetic neuropathy prevalence varies depending on how long you've had the disease. When individuals with T2DM were followed for ten years, the prevalence of diabetic neuropathy increased from 8% to 42%[29]. Patients with newly diagnosed screen-detected T2DM33 had a 13 percent prevalence of diabetic neuropathy at study entrance, with a cumulative incidence of 10% throughout the 13-year follow-up period in a cohort with very mild T2DM who adhered to good metabolic management in the Danish Addition trial. In the BARI 2D trial, 50 percent of patients with more advanced T2DM and proven coronary artery disease had confirmed diabetic neuropathy at baseline[27], and the 4-year cumulative incidence of diabetic neuropathy was 66–72 percent in those who did not have neuropathy at baseline[27]. Given how common neuropathy is in individuals with diabetes, effective diagnostic, screening and prevention strategies are of paramount importance.

Symptoms of DN

Positive sensory symptoms (excessive response to a stimulus or spontaneously) such as paresthesia and pain are present in the majority of symptomatic patients, and proprioceptive ataxia may be present in some cases. Numbness, tingling, instability, and falls, as well as shocks, pricks, and, in particular, scorching, are examples of these feelings. They are seen in the lower extremities (LLll) and can progress to the upper extremities (UULL), with patients reporting worsening at night. These are usually minor symptoms, although they can become severe and incapacitating. Loss of sensitivity in the affected segment is associated with negative sensory symptoms (decreased response to a specific stimulus).

There is distal hypoesthesia/hyperesthesia in segments during neurologic examination, initially in thermoalgesic sensitivity modalities. There may be hyperesthesia (exaggerated response to tactile stimuli), hyperalgesia (exaggerated sensitivity to painful stimuli), hyperpathia (pain persistence even after painful stimulus removal), or even allodynia in the case of acute painful neuropathy (painful sensation caused by painless stimuli). Tactile,

vibratory, and proprioceptive hypo/anaesthesia are examples of deep sensitivity hypo/anaesthesia. In addition, when extensive fibres sensory damage occurs, there is deep hypo/ arreflexia, primarily in the Achillean reflex, and in severe cases, there may be worldwide areflexia[34].

Types of DN

Asymmetrical/Focal and Multifocal Presentations

Acute mononeuropathies

They relate to the sudden onset of a nerve's affection, which is usually accompanied by sensory (pain and paresthesia) and motor symptoms in the area served by that neuron. It is more common in older people, with vascular blockage as the primary cause, resulting in ischemia of nerve fibres.

In most cases, it has a self-limited course and a satisfactory clinical treatment, with a six- to eight-week recovery time. It's more common in cranial nerves such the oculomotor, trochlear, and facial nerves, as well as peripheral nerves like the ulnar and fibular[35 23].

Chronic compressive mononeuropathies

They begin slowly with sensory symptoms and progress to motor involvement in compression sites such as the wrist median nerve (Carpal Tunnel syndrome - CTS), elbow ulnar, common fibular in the fibular head, and lateral and medial plantar nerves in tarsal tunnel syndrome.

Their prevalence is three times that of the general population, with micro traumas linked to perineural edoema caused by DM metabolic alterations peaking in nerve compression as the pathophysiology. Its course is often progressive, and it might present with severe motor manifestations that necessitate surgical intervention[35].

Radiculoplexus neuropathies (RPNP)

Asymmetrical sensory-motor presentations with proximal and distal segments characterise RPNP. In up to 50% of patients, they appear with severe and disabling painful symptoms and may present with autonomic symptoms[36]. They can affect the cervico-brachial, thoracic, abdominal, or lumbosacral segments separately or simultaneously[37]. Said et al.[38] and Dyck, Norell, and Dyck[37] found indications of microvasculitis and subsequent ischemia injury in LLll peripheral nerve biopsies, suggesting that their pathogenesis is linked to immunopathic processes.

Despite the severity of the involvement of nerve fibres, the prognosis is often excellent, even without therapeutic intervention. In the literature, however, it is still unclear whether immunomodulators such as steroids, intravenous human immunoglobulin (IgIV), or plasmapheresis are effective[36].

Symmetrical/Diffuse Presentations

Insulinic neuritis

Carvati[39] was the first to report this, after observing patients with distant sensory problems in LLII after starting insulin medication. It has an unclear pathophysiologic mechanism and a generally benign course.

Hypoglycaemic neuropathy

Uncommon condition caused by extended and recurring hypoglycemia episodes, usually caused by insulinomas (insulin-producing pancreatic tumor). It has a sensory-motor pattern, a predominance of upper limbs (UULL), and atrophy, and it may be reversible once the hypoglycemia condition is treated[40,41].

Post-ketoacidosis polyneuropathy

The CNS symptoms of ketoacidosis, an acute consequence of glycemic decompensation reported by DM type 1 patients in general, are well-known. However, PNS participation is not only unusual, but it is also poorly understood. Case studies of these disorders suggest that motor polyneuropathy is the most common presenting symptom, with quick and spontaneous recovery upon reversion of this core condition[36].

Acute painful sensory neuropathy

Diabetic cachexia neuropathy is a condition that develops after a significant weight loss as a result of uncontrolled DM glycemia. It progresses in a single phase, starting with an initial onset of symptoms on LLll, which are typically painful, severe, and disabling. Because of the significant link between glycemic uncontrol and the development of this neuropathy, metabolic alterations may play a role in its pathogenesis, but these processes have yet to be fully described. Glycemia and pain control are used to treat it. It has a positive prognosis as pain and weight gain reduce following glycemic control[42].

Glucose intolerance-associated neuropathy

For a long time, this was a controversial clinical entity until Lu et al.[43] demonstrated glucose intolerance as an independent risk factor for PN in a large population research. It is characterised by sensory and autonomic symptoms, with tiny fibres also being involved. It shares the same pathophysiologic processes as DSP, implying that this is a kind of DM that has already developed.

Autonomic neuropathy (AN)

Small PNS unmyelinated fibres (C fibres) are involved in a disorder that affects the autonomic nervous system as

a result of chronic hyperglycemia metabolic alterations. DM and pre-diabetes autonomic neuropathy can occur in isolation on rare occasions. It is assumed to be part of the same spectrum of chronic disease as DM[44] in the vast majority of cases. It develops concurrently with other DN kinds, most typically with DSP.

Although only 14 percent of patients with DM type 1 and 70 percent of patients with DM type 2 have moderate to severe disease[44], it is predicted that 50 percent of patients with DM type 1 and 70 percent of patients with DM type 2 have some autonomic involvement.

The cardiovascular, gastrointestinal, and urogenital systems, as well as sudomotor function and pupillary motility, may be affected by AN.

Autonomic cardiovascular dysfunction has been well recognised as an independent risk factor for mortality secondary to cardiovascular disease[45,46], and has been linked to an increased risk of post-surgical complications and mortality[47,48]. Postural hypotension, arrhythmias, silent myocardial ischemia, pressure lability, and exercise intolerance are some of the most common symptoms[45].

In diabetic AN, sensory, motor, and secretory systems of the gastrointestinal system may be affected, resulting in symptoms such as nausea, early society, vomiting, diarrhoea-constipation alternation, and, in more severe instances, postprandial hypotension and syncope[49].

Erectile dysfunction may be the first symptom of autonomic DN alterations, although also shares additional pathogenic pathways with other autonomic DN changes, such as internal pundendal artery atherosclerosis. It has a significant emotional impact, resulting in a significant reduction in quality of life[50].

Diabetic cytopathy is characterised by urinary problems induced by alterations in detrusor smooth muscles and urothelial dysfunction as a result of autonomic urogenital system involvement. Dysuria, polaciuria, nocturia, urine urgency, and inadequate bladder emptying are the most common symptoms. These factors, added to DM-related immunosuppression, increase the prevalence of repetitive urinary tract infections, contributing to the development of renal failure among these patients[51].

Sudomotor dysfunction causes trophic alterations in the limbs in diabetic AN, which are linked to Charcot arthropathy, LLll ulcers, and amputations. Changes in LLll colour and distal temperature are common symptoms, along with hair loss, heat sensitivity, skin dryness, reduced sweating, and perforating plantar disease[52].

There are pupillary changes that are not uncommon, such as the presence of an Argyll Robertson pupil, which is characterised at exam by shrinking and presenting dissociations between light and convergence reactions, that is, they react weakly or not at all to light while reacting very well to proximity. This is because parasympathetic fibres of the oculomotor nerve are involved[53].

Distal symmetrical polyneuropathy (DSP)

Because it is the most frequent type of DN, it is predicted to be present in 50% of both type 1 and type 1 diabetec patients, and it is already present in 20% of patients when they are diagnosed with DM. In most circumstances, it remains subclinical, with only around half of DSP patients becoming symptomatic.

It progresses slowly, symmetrically, showing sensory and autonomic symptoms with a predominance of small fibre involvement, progressing with sensory big fibre involvement and finally motor fibre involvement in its more severe stages. It is traditionally distally dispersed in LLll, progressing length-dependently to the upper limbs (UULL), central abdominal area, and vortex, in a pattern known as "socks, gloves, and apron."

It has been linked to various types of DN, particularly chronic compressive mononeuropathies like CTS, but it has also been linked to inflammatory neuropathies like chronic inflammatory unmyelinating polyradiculopathy in some cases (CIUP). Although there is no obvious direct relationship between the two disorders, persistent peripheral nerve involvement by DM appears to be a risk factor for its development. [42].

Pathogenesis of DM

Multiple variables linked to metabolic, vascular, inflammatory, and neurodegenerative processes are linked to DSP aetiology. Chronic hyperglycemia plays a significant role in DSP pathogenic pathways and is the primary triggering factor[54].

receptors for AGEs.

Metabolic pathway

Peripheral nerves absorb a lot of glucose, which causes a variety of pathologic metabolic reactions. The polyol pathway, for example, involves the aldose reductase enzyme, which converts glucose to sorbitol. The accumulation of sorbitol and fructose within cells reduces the active transit of numerous metabolites, including myo-inositol.

This process alters intracellular regulatory mechanisms, resulting in a decrease in Na/K pump function and an increase in intracellular sodium concentration. This causes a rise in intracellular osmolarity, which causes oxidative stress. The initial and reversible structural changes in Ranvier nodes are caused by these anomalies,

which lower nerve conduction velocity.

Another pathologic metabolic pathway resulting from persistent hyperglycemia is the creation of final advanced glycosylation products (FAGP), which are formed by a non-enzymatic interaction between amino acid groups and glucose reduction products.

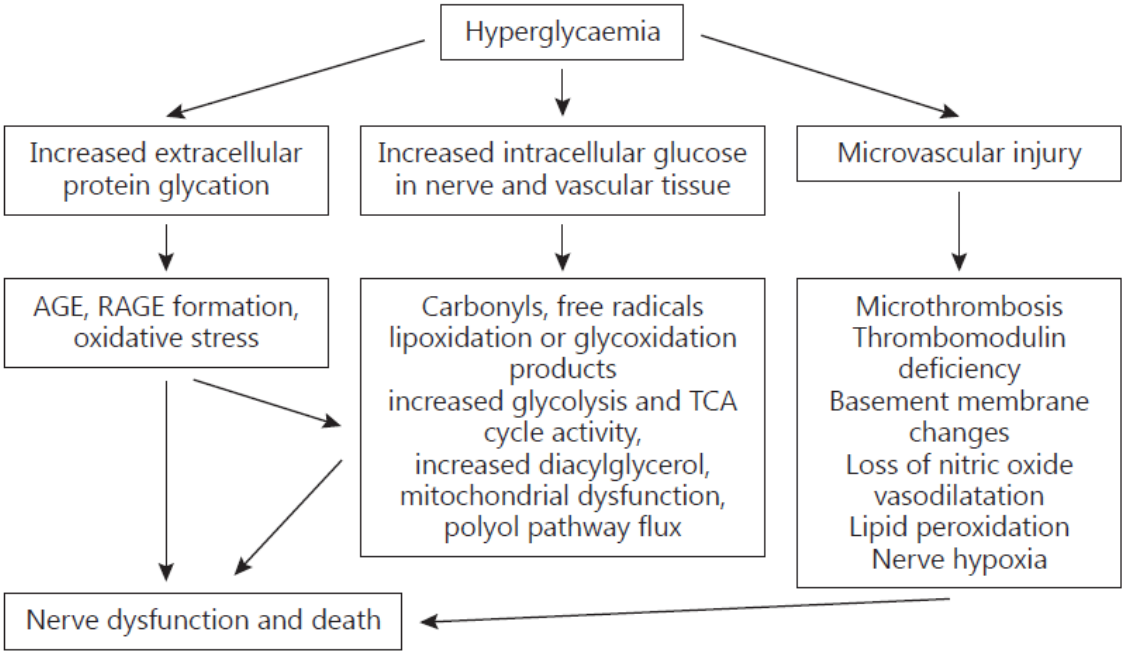

Fig.1. The pathogenesis of diabetic neuropathy [based on 5].

AGE = Advanced glycation end product; RAGE = FAGP affects intracellular function of many proteins, as well as extracellular components like laminin and fibronectin, which are required for axonal regeneration, and promotes irreversible binding in macrophage and endothelial cell receptors. Oxidative stress, cytokine release, and extracellular matrix disintegration occur as a result of these alterations, culminating in cell apoptosis.

High glucose levels also increase excessive protein C kinase activation, which controls the generation of nitric oxide, which causes ischemic peripheral nerve injury[55].

Due to the high rate of linkage between DM and dyslipidemia (DLD)[56], it has recently been discovered that excessive lipids play a role in DN pathogenesis[57]. Direct damage of free fatty acids in Schwann cells has been demonstrated in vitro[58] [46]. Furthermore, systemic DLP effects boost the production of pro-inflammatory compounds and oxidative stress.

The activation of the hexosamine pathway, which is induced by hyperglycemia, leads in alterations in the expression of specific genes and the functioning of intracellular proteins[59], is linked to all of these metabolic pathways.

The polyol pathway, as well as FAGP and protein kinase C, promote the generation of free radicals in response to oxidative stress. This pathway causes mytochondrial malfunction, which initiates the cell apoptotic cascade[55] when it is severely harmed.

Vascular pathway

Based on the observation of decreased blood flow, increased vascular resistance, and decreased oxygen tension, generalised nerve microvascular dysfunction has been proposed as a pathogenic cause. Endoneural microvascular anomalies such as basal membrane thickening and duplication, edoema, endothelial and intimal smooth muscle growth, and the presence of occlusive platelet clot[54] have all been documented.

Neurodegenerative pathway

Loss of cell neurotrophism is another factor that could be involved in DN pathogenesis. In diabetes, a decrease in the quantity and quality of insulin causes a partial reduction in the activity of insulin-like growth factor I and neuronal growth factor, resulting in a decrease in the production of proteins necessary for the formation of neurofilaments and the maintenance of axonal transport, both of which are required for their growth and regeneration. Axonal degeneration and neuronal body death occur as a result, causing neuropathy to develop gradually[55].

Inflammatory pathway

There is strong evidence that the development of DN is mediated by an immunopathic mechanism. In diabetic patients with neuropathy, pro-inflammatory drugs have been found to promote inflammatory cell recruitment, cytokine production, and reduced blood flow60. In conclusion, these pathways exacerbate peripheral nerve hypoxia and ischemia, making regeneration more difficult[61].

Histopathologic Changes

Electronic microscopy revealed poorly aligned filaments in the subaxolemal area, indicating that axonal transit has slowed. These neurofilaments are eventually scavenged by Schwann cells, which, when combined with a drop in cytoskeleton protein production, results in a decrease in axonoplasmatic volume, causing axonal atrophy to peak with Wallerian degeneration.

As a result, the most prevalent affection pattern is compatible with dying-back axonal degeneration, which mostly affects longer fibres, resulting in a length-dependent clinical pattern. These variables cause the most significant DN histopathologic change: multifocal nerve fibre loss, with axonal degeneration in activity and, depending on the severity of the disease, some level of regeneration, as seen by sproutings. There are also destroyed blood vessels with endothelial basal thickening and neoangiogenesis, indicating that the ischemia component is present. It is also possible to observe segmentar demyelination and remyelination, which reflects the mixed neurophysiologic involvement pattern (axonal and unmyelinating) of this condition[62].

Diagnosis of DN

Over the years, several clinical scales and other tests have been proposed to detect DPS early and track its evolution in terms of PNS involvement. Neurophysiologic, autonomic, and morphologic studies should be prioritised among additional tests.

Neurophysiologic Tests

Electroneuromyography (ENMG)

For DSP diagnosis, ENMG has remained the gold standard. It is still the most widely used and available diagnostic procedure in Brazil today. Despite the test's inability to detect early involvement of small fibres in this condition, it is critical to assess not only the involvement of large fibres but also the symmetry, severity, and progression of the disease, ruling out other coexisting conditions like myopathy, motor plate or inferior motor neuron diseases, as well as primary demyelinating diseases like PIDC or hereditary neuropathies. It is feasible to characterise both the time of evolution (acute versus chronic) and the spread of neurophysiologic changes using a needle test (electromyography - EMG).

Motor evaluation of the median, ulnar, tibial, and fibular nerves, as well as sensory evaluation of the median, ulnar, radial, and sural nerves, are part of the regular neuroconduction investigation in diabetic patients with DSP. When a differential diagnosis with additional etiologies is required, an EMG should be performed63.

It usually manifests as a pure sensory or sensory-motor polyneuropathy, or as a mixed polyneuropathy with axonal and distal predominance, affecting LLll. Sensory abnormalities in distal LLll nerves with lower sensory action potential amplitude in plantar, superficial fibular, and sural nerves are the first changes seen in DSP patients' neuroconduction. The disease advances with sensory UULL involvement and a 10 to 30% drop in conduction velocities (first of LLll advancing to UULL) until it presents diminished compound muscle action potentials (CMAP) with a preponderance of LLll[64,65 57,58] in its most severe phases.

In some nerves susceptible to compression, such as the wrist median, elbow ulnar, and common fibular nerves of the fibular head, there is often a focal slowing of conduction velocity with possible presence of conduction blockade (more than 50% decrease in CMAP amplitude from a proximal stimulation point to a distal stimulation point).

Although exceedingly beneficial, this test has several drawbacks, including patient pain, low sensitivity in detecting early illness symptoms (tiny fibres), and the need for specialist personnel and equipment[66].

Quantitative sensitivity test (QST)

Thermal, painful, and vibratory modalities were employed to identify and quantify sensory abnormalities in polyneuropathy. It can be done at various locations by administering thermal hot and cold stimuli and monitoring the temperature at the point when patients begin to feel the stimulus and pain. It is also feasible to measure the amount of vibration that patients are exposed to.

It is a useful tool in clinical practise since it is a quick, noninvasive, and simple diagnostic. This procedure, however, has a low rate of repeatability since it relies on patients' cooperation, attention, and drive, and the results are sensitive to emotional status. Furthermore, this test catches changes in any position of the neuraxis, which might lead to analysis errors[63].

Evoked potentials

Evoked potentials are the electric reactions of the central nervous system to an external stimulus[67]. Laser evoked

potential stimulation (LEPS) and contact heat evoked potential stimulation (CHEPS) are two techniques for studying tiny fibre polyneuropathy (CHEPS). These techniques allow researchers to look at the peripheral and central conduction of A and C fibres. LEPS, on the other hand, may induce skin damage in laser-stimulated areas, whereas CHEPS is noninvaise and capable of generating repeatable evoked potentials, in addition to being more sensitive and specific. There is presently no clinical practise standardisation for both methods[68].

Autonomic tests

There are numerous autonomic tests that can be used to determine whether C fibres are involved. In clinical practise, the tilt test, Valsalva manoeuvre, and R-R interval calculation at ECG, and the reflex sympathetic skin response and sudomotor reflex quantitative test, respectively, are the most accessible tests for cardiac and sudomotor evaluation.

Morphologic Tests

Nerve biopsy

For a long time, peripheral nerve biopsy was employed to investigate the morphology and pathophysiology of nerve fibre involvement in DN[69]. Because this is an intrusive test with the potential for difficulties and sequelae, it is currently reserved for atypical clinical presentations where the overlapping with other etiologies, such as inflammatory/infectious neuropathies and amyloidosis, is unclear. Furthermore, examining the blades70 demands extremely specialised material and trained professionals. In general, fascicular biopsy of the superficial sensory nerve is preferred in research because it is less damaging.

Skin biopsy

It is feasible to identify small epidermal nerve fibres with a fragment of around 3mm of hairless skin obtained by punch biopsy, making it a helpful tool for diagnosing small fibres neuropathy. This method is based on immune-hystochemical staining of PGP 9.5 – a protein gene product found throughout nerve fibre extension that allows for direct observation of epidermal fibres.

Currently, intraepidermal fibre density quantification from skin biopsy is recommended as a diagnostic approach for small fibre neuropathy, and it has been published with gender and age standardisation. Its drawbacks include the fact that it is an invasive procedure that provides no additional information about the cause of the neuropathy[71].

Confocal corneal microscopy

The human cornea sub-basal plexus, which is made up of small fibres, has recently been mapped in vivo using confocal microscopy, allowing for its characterisation and distribution pattern of nerve fibres in healthy people of both genders and ages.[72]

Malik et al.[73] [66] used corneal confocal microscopy (CCM) in vivo to show for the first time, in a series of 18 diabetic patients compared to controls, a substantial decrease in sub-basal plexus fibres, highlighting this test as a quick, noninvasive, and repeatable diagnostic method to identify DSP.

Since then, this approach has been shown in a number of trials to be capable of detecting neuropathy, as well as disease progression and prospective therapeutic improvement.

Treatment of DN

Glycemic management appears to be crucial for DN[74] stabilisation and even improvement. All efforts should be made to keep patients normoglycemic in this manner. Several evidences suggest that oxidative stress has a role in DN formation.

Antioxidant medications would therefore be an ideal treatment option. Intravenous -lipoic acid (thioctacideMR) (600mg/day for 3 weeks) is now the only disease-based treatment that has been shown to be effective and may be used in clinical practice[78]. The same medicine, taken orally (600 mg per day in fasting), is the only form now available in Brazil, and more evidence is needed to confirm its efficacy[74] [67]. Other therapy options have been offered, but there is still no evidence that these are effective[74].

Tricyclic antidepressants, anticonvulsants gabapentin and pregabalin, and antidepressant duloxetine, a selective dual inhibitor of serotonin and norepinephrine reuptake, are among the current medications for the treatment of symptomatic pain. Second-line evidence supports the use of opioids such tramadol and oxycodone[74]. Before utilising opioids, a combination of first-line medicines should be considered[74].

Tricyclic antidepressants have demonstrated efficacy, but their side effects, which include xerostomy, perspiration, dizziness, drowsiness, urine retention, and glaucoma, are key limiting issues. Their usage above 100mg/day appears to be linked to an increased risk of sudden death, which is why they should be administered with caution in cardiopathic patients. Starting with 10 to 25mg/day and progressively increasing the dose with careful patient monitoring is recommended. Although doses up to 150mg/day are recommended, it is difficult to go higher than 75mg/day. The patient's symptoms as well as the drug's side effects should be considered before selecting a certain drug[74].

Gabapentin and pregabalin, both calcium channel alpha-2-delta subunit inhibitors, are now the best anticonvulsants for this group of patients[74]. Duloxetine, relative to venlafaxine, had the best cost-benefit and control of painful neuropathy[76] among dual antidepressants, serotonin and norepinephrine reuptake blockers. Duloxetine can be started at 30 mg/day and gradually increased to 60 mg/day over the course of a week. To control NP, some people require 120mg every day.

Decompressive procedures are theoretically justified whenever there is clinical and/or electromyographic evidence of severe arrest with large motor involvement; nonetheless, the risk of no improvement or even deterioration is significant and should be emphasised to patients. Orienting prevention and treatment of diabetic foot, which results in insensitivity and autonomic dysfunction, is perhaps one of the most significant functions of neurologists in managing DN. Periodic exams, self-evaluation orientation, and prompt rest at the outset of any injury are all simple but crucial precautions to take.

IV.CONCLUSION

In the subject of diabetic neuropathy, there is a clear call to action. Effective medicines to prevent and treat diabetic neuropathy are urgently needed as the diabetes and obesity pandemic continues to spread. Due to our lack of basic understanding of diabetic neuropathy, prominent pharmaceutical corporations have decreased research and clinical trials in this illness. Despite the disease's increasing burden, this change has occurred. Only the individual expenses to each patient, such as discomfort, inability to work, low QOL, frequent hospitalizations for ulcers, and eventual amputations, surpass the social costs of diabetic neuropathy. Despite the fact that diabetic neuropathy is the most powerful predictor of mortality in T2DM, it is the only microvascular consequence of diabetes that does not have a specific treatment. Accumulating clinical and preclinical research in the next decade can and will change this scenario.

REFERENCES

1. International Diabetes Federation. (2009). Diabetes Atlas, 4th ed, International Diabetes Federation.
2. Tripathi KD, editor. Essentials of medical pharmacology.6th ed. New Delhi: Jaypee brothers medical publishers, 2008.
3. http://emedicine.medscape.com/article/1170337-overview#a0101 (12 Dec.2011)
4. http://en.wikipedia.org/wiki/Diabetic_foot (12 Dec.2011)
5. http://www.expresshealthcare.in/201001/knowledge02.shtml (12 Dec.2011)
6. Roy Taylor, Lorrane Agius.The biochemistry of diabetes. Biochem. J.1988;250: 625-40.
7. Lance S. Weinhardt, Michael P. Carey. Prevalence of erectile disorder in men with diabetes mellitus : Comprehensive review, methodological critique, and suggestions for future research. The Journal of Sex Research.1996; 33(3): 205-14.
8. Cusi K. Nonalcoholic fatty liver disease in type 2 diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2009;16(2):141-9
9. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology. (1993) 43:817– 24. doi: 10.1212/WNL.43.4.817
10. Albers JW, Pop-Busui R. Diabetic neuropathy: mechanisms, emerging treatments, and subtypes. Curr Neurol Neurosci Rep. (2014)14:473. doi: 10.1007/s11910-014-0473-5
11. Dietrich I, Braga GA, de Melo FG, da Costa Silva Silva ACC. The diabetic foot as a proxy for cardiovascular events and mortality review. Curr Atheroscler Rep. (2017) 19:44. doi: 10.1007/s11883-017- 0680-z
12. Vadiveloo T, Jeffcoate W, Donnan PT, Colhoun HC, McGurnaghan S, Wild S, et al. Amputation-free survival in 17,353 people at high risk for foot ulceration in diabetes: a national observational study. Diabetologia. (2018) 61:2590–7. doi: 10.1007/s00125-018-4723-y
13. Alleman CJ, Westerhout KY, Hensen M, Chambers C, Stoker M, Long S, et al. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: a review of the literature. Diab Res Clin Practice. (2015) 109:215–25. doi: 10.1016/j.diabres.2015.04.031
14. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med. (2017) 376:2367–75. doi: 10.1056/NEJMra 1615439
15. Sloan G, Shillo P, Selvarajah D, Wu J, Wilkinson ID, Tracey I, et al. A new look at painful diabetic neuropathy. Diab Res Clin Pract. (2018) 144:177– 91
16. Sadosky A, Mardekian J, Parsons B, Hopps M, Bienen EJ, Markman J. Healthcare utilization and costs in diabetes relative to the clinical spectrum of painful diabetic peripheral neuropathy. J Diabetes Complications. (2015) 29:212–7
17. Kioskli K, Scott W, Winkley K, Kylakos S, McCracken LM. Psychosocial factors in painful diabetic neuropathy: a systematic review of treatment trials and survey studies. Pain Med. (2019) 20:1756–73.
18. Callaghan BC, Little AA, Feldman EL, Hughes RA (2012) Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev (6):CD007543.
19. Callaghan BC, Price RS, Feldman EL (2015) Distal Symmetric Polyneuropathy: A Review. JAMA 314(20):2172–2181.

20. Pop-Busui, R. et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* **40**, 136–154 (2017).
21. Gordois, A., Scuffham, P., Shearer, A., Oglesby, A. & Tobian, J. A. The health care costs of diabetic peripheral neuropathy in the US. *Diabetes Care* **26**, 1790–1795 (2003).
22. Italian General Practitioner Study Group (IGPSG). Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions. I. Prevalence and general characteristics of the sample. *Neurology* **45**, 1832–1836 (1995).
23. Bharucha, N. E., Bharucha, A. E. & Bharucha, E. P. Prevalence of peripheral neuropathy in the Parsi community of Bombay. *Neurology* **41**, 1315–1317 (1991).
24. Callaghan, B. C. et al. Role of neurologists and diagnostic tests on the management of distal symmetric polyneuropathy. *JAMA Neurol.* **71**, 1143–1149 (2014).
25. Ang, L., Jaiswal, M., Martin, C. & Pop-Busui, R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr. Diab. Rep.* **14**, 528–0528 (2014).
26. Martin, C. L., Albers, J. W. & Pop-Busui, R. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* **37**, 31–38 (2014).
27. Pop-Busui, R. et al. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Cohort. *Diabetes Care* **36**, 3208–3215 (2013).
28. Franklin, G. M., Kahn, L. B., Baxter, J., Marshall, J. A. & Hamman, R. F. Sensory neuropathy in non-insulin-dependent diabetes mellitus. The San Luis Valley Diabetes study. *Am. J. Epidemiol.* **131**, 633–643 (1990).
29. Partanen, J. et al. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N. Engl. J. Med.* **333**, 89–94 (1995).
30. Dyck, P. J. et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* **43**, 817–824 (1993).
31. Boulton, A. J., Knight, G., Drury, J. & Ward, J. D. The prevalence of symptomatic, diabetic neuropathy in an insulin-treated population. *Diabetes Care* **8**, 125–128 (1985).
32. Tesfaye, S. et al. Vascular risk factors and diabetic neuropathy. *N. Engl. J. Med.* **352**, 341–350 (2005).
33. Andersen, S. T. et al. Risk factors for incident diabetic polyneuropathy in a cohort with screen-detected type 2 diabetes followed for 13 years: ADDITION-Denmark. *Diabetes Care* **41**, 1068–1075 (2018).
34. Sinnreich M, Taylor BV, Dyck PJ. Diabetic neuropathies. Classification, clinical features and pathophysiological basis. Neurologist. 2005;11(2):63-79.
35. Vinik AI, Mehrabyan A. Diabetic neuropathies. Med Clin North Am. 2004;88(4):947-99
36. Dyck PJ, Windebank AJ. Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. Muscle Nerve. 2002;25(4):477-91
37. Dyck PJ, Norell JE, Dyck PJ. Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy. Neurology. 1999;53(9):2113-21.
38. Said G, Goulon-Goeau C, Lacroix C, Moulonguet A. Nerve biopsy findings in different patterns of proximal diabetic neuropathy. Ann Neurol. 1994;35(5):559-69
39. Carvati C. Insulin neuritis: a case report. Va Med Mon. 1933;59:745-6.
40. Jaspan JB, Wollman RL, Bernstein L, Rebenstein AH. Hypoglycemic peripheral neuropathy in association with insulinoma: Implication of glucopenia rather than hyperinsulinism. Case report and literatura review. Medicine. 1982;61(1):33-44.
41. de Freitas MR, Chimelli L, Nascimento OJ, Barbosa GM [Hypoglycemic polyneuropathy: report of a case with insulinoma]. Arq Neuropsiquiatr. 1989;47(2):235-40. Portuguese.
42. Sinnreich M, Taylor BV, Dyck PJ. Diabetic neuropathies. Classification, clinical features and pathophysiological basis. Neurologist. 2005;11(2):63-79.
43. Lu B, Hu J, Wen J, Zhang Z, Zhou L, Li T, Hu R. Determination of peripheral neuropathy prevalence and associated factors in Chinese subjects with diabetes and pre-diabetes - ShangHai Diabetic Neuropathy Epidemiology and Molecular Genetics Study (SH-DREAMS). PLoS One. 2013;8(4) e61053.
44. Low PA, Benrud-Larson LM, Sletten DM, Opfer-Gehrking TL, Weigand SD, O'Brien PC, et al. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care. 2004;27(12):2942-7.
45. Vinik AI. Diabetic autonomic neuropathy. Diabetes Care. 2003;26:1553-79.
46. Suarez GA, Clark VM, Norell JE, Kottke TE, Callahan MJ, O'Brien PC, et al. Sudden cardiac death in diabetes mellitus: risk factors in the Rochester diabetic neuropathy study. J Neurol Neurosurg Psychiatry. 2005;76(2):240-5.
47. Burgos LG, Ebert TJ, Asiddao C, Turner LA, Pattison CS, Wang-Cheng R, et al. Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. Anesthesiology. 1989;70(4):591-7, 1989.
48. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care. 2003;26(6):1895-901.
49. Rayner CK, Horowitz M. Gastrointestinal motility and glycemic control in diabetes: the chicken and the egg revisited? J Clin Invest. 2006;116(2):299–302.
50. Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. J Sex Med. 2009;6(5):1232-47.
51. Hill SR, Fayyad AM, Jones GR. Diabetes mellitus and female lower urinary tract symptoms: a review. Neurourol Urodyn. 2008;27(5):362-7.
52. Tentolouris N, Marinou K, Kokotis P, Karanti A, Diakoumopoulou E, Katsilambros N. Sudomotor dysfunction is associated with foot

ulceration in diabetes. Diabet Med. 2009;26(3):302-5.
53. Smith AG, Singleton JR. Diabetic neuropathy. Continuum. 2012;18(1):60-84.
54. Zochodne DW. Diabetes mellitus and the peripheral nervous system: manifestations and mechanisms. Muscle Nerve. 2007;36(2):144-66.
55. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. Pharmacol Ther. 2008;120(1):1-34.
56. Clemens A, Siegel E, Gallwitz B. Global risk management in type 2 diabetes: blood glucose, blood pressure, and lipids--update on the background of the current guidelines. Exp Clin Endocrinol Diabetes. 2004;112(9):493-503.
57. Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes. 2009;58(7):1634-40
58. Padilla A, Descorbeth M, Almeyda AL, Payne K, De Leon M. Hyperglycemia magnifies Schwann cell dysfunction and cell death triggered by PA-induced lipotoxicity. Brain Res. 2011;1370:64-79.
59. Farmer KL, Li C, Dobrowsky RT. Diabetic peripheral neuropathy: should a chaperone accompany our therapeutic approach? Pharmacol Rev. 2012;64(4):880-900.
60. Gruden G, Bruno G, Chaturvedi N, Burt D, Schalkwijk C, Pinach S, et al. Serum heat shock protein 27 and diabetes complications in the EURODIAB prospective complications study: a novel circulating marker for diabetic neuropathy. Diabetes. 2008;57(7):1966-70.
61. McDonald DS, Cheng C, Martinez JA, Zochodne DW. Regenerative arrest of inflamed peripheral nerves: role of nitric oxide. Neuroreport. 2007;18(16):1635-40.
62. Yasuda H, Dyck PJ. Abnormalities of endoneurial microvessels and sural nerve pathology in diabetic neuropathy. Neurology. 1987;37(1):20-8.
63. Perkins BA, Bril V. Diabetic neuropathy: a review emphasizing diagnostic methods. Clin Neurophysiol. 2003;114(7):1167-75.
64. Redmond JM, McKenna MJ, Feingold M, Ahmad BK. Sensory testing versus nerve conduction velocity in diabetic polyneuropathy. Muscle Nerve. 1992;15(12):1334-9.
65. Albers JW, Brown MB, Sima AA, Greene DA. Nerve conduction measures in mild diabetic neuropathy in the Early Diabetes Intervention trial: the effects of age, sex, type of diabetes, disease duration, and anthropometric factors. Neurology. 1996;46:85-91 1996;46(1):85-91.
66. Wooten K. Clinical features and eletrocdiagnosis of diabetic peripheral neuropathy in the dysvascular patients. Phys Med Rehabil Clin N Am. 2009;20(4):657-76.
67. American EEG Society. Clinical evoked potentials guidelines: recommended standards for normative studies of evoked potentials, statistical analyses of results and criteria for clinically significant abnormality. J Clin Neurophysiol. 1994;11(1):45-47.
68. Casanova-Molla J, Grau-Junyent JM, Morales M, Valls-Solé J. On the relationship between nociceptive evoked potentials and intraepidermal nerve fiber density in painful sensory polyneuropathies. Pain. 2011;152(2):410-8.
69. Sima AA. Diabetic neuropathy--the utility of nerve biopsy. Eletroencephalogr Clin Neurophysiol Suppl. 1999;50:525-33.
70. Thomas PK. Nerve biopsy. Diabet Med. 1997;14(5):345-6.
71. Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol. 2010;17(7):903-12.
72. Oliveira-Soto L, Efron N. Morphology of corneal nerves using confocal microscopy. Cornea. 2001;20(4):374-84.
73. Malik RA, Kallinikos P, Abbott CA, van Schie CH, Morgan P, Efron N, et al. Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. Diabetologia. 2003;46(5):683-8.
74. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33(10):2285-93.
75. Ziegler D. Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review. Treat Endocrinol. 2004;3(3):173-89.
76. Wu EQ, Birnbaum HG, Mareva MN, Le TK, Robinson RL, Rosen AM, et al. Cost-effectiveness of duloxetine versus routine treatment for U.S. patients with diabetic peripheral neuropathic pain. J Pain. 2006;7(6):399-407.