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NEW PERSPECTIVES ON DIABETIC PERIPHERAL NEUROPATHY AND THE ROLE OF GLYCEMIC CONTROL

Dr Jayesh Patil[1], Dr Ashok Kumar[2]

From Department of General Medicine, Santosh Deemed to be University

ABSTRACT:

Diabetes mellitus is characterized by elevated blood sugar, which results in numerous macrovascular and microvascular complications. Additionally, it is a known cause of peripheral neuropathy (PN). This evaluation illustrates the significance of peripheral neuropathy detection in clinical practice. Neuropathy is a common and expensive consequence of both type 1 and types 2 diabetes. Neuropathy is predicted to present in approximately 8% of newly diagnosed individuals and over 50% of people with chronic illnesses. Diabetes neuropathy symptoms may manifest as somatic, autonomic, motor, or sensory problems. The most prevalent type of distal sensory polyneuropathy affects the distal lower extremities and hands in a "glove and stocking" pattern. This article examines advances that facilitate the early detection of DPN and evaluates the evidence for early multiple risk factor management techniques to ameliorate DPN.

Keywords: Diabetes, Neuropathy, glycemic control, sensory polyneuropathy

INTRODUCTION:

Diabetes mellitus is characterized by elevated blood glucose levels, which leads to a variety of macrovascular and microvascular complications. This analysis demonstrates the significance of peripheral neuropathy detection in clinical practice. Neuropathy is a common and expensive consequence of diabetes type 1 and types 2 [1]. Somatic, autonomic, motor or sensory problems may develop as diabetic neuropathy. The most common kind of distal sensory polyneuropathy affects the distal lower extremities and hands in a "glove and stocking" pattern. Cardiac autonomic neuropathy can contribute 6% of sudden fatalities (painless myocardial infarction) in long-term diabetics [2].

Even sensory, motor, or autonomic neuropathy can result in fissures or calluses, leading to ulceration. The most debilitating outcome of gastrointestinal autonomic neuropathy is gastroparesis, while genitourinary autonomic neuropathy can result in sexual dysfunction and neurogenic bladder. Only strict glucose control has been shown to prevent and slow the progression of diabetic peripheral neuropathy and autonomic neuropathy.

All patients with type 2 diabetes should be examined for diabetic neuropathy commencing at the time of diagnosis, five years after the diagnosis of type 1 diabetes, and annually after that.

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Symptomatic treatment for sensory symptoms includes tricyclic antidepressants, serotonin, norepinephrine reuptake inhibitors, gabapentin, pregabalin, and opioids [3]. Other management strategies are impractical.

DEFINITION, STAGES, AND CLASSIFICATION OF DIABETIC NEUROPATHY:

***CLINICAL NEUROPATHY:** neuropathy clinical symptoms with abnormal quantitative neurological function tests (e.g., sensory or autonomic function tests, electrophysiological tests).

***SUBCLINICAL NEUROPATHY:** An abnormal quantitative neurological function test that is mostly sensory and minimal or no clinical neuropathy symptoms on examination.

***Mayo Clinic clinical criteria and staging for diabetic neuropathy:**

Stage	Features	Symptoms and signs	Sensory tests (quantitative) abnormal
0	No neuropathy	NO	NO
1	Subclinical Neuropathy	NO	Yes
2	Clinically evident neuropathy	Yes	Yes
3	Debilitating Neuropathy	Yes	Yes

CLASSIFICATION OF DIABETIC NEUROPATHY-

Distalsymmetrical polyneuropathy (DSPN) is the most common form.

SymmetricPolyneuropathy	*AsymmetricFocal and multifocal neuropathies*
**Distal sensory polyneuropathy* **Autonomic neuropathy*	*Cranial neuropathy *Limb mononeuropathy *Compression and entrapment neuropathy - femoral, sciatic, ulnar, peroneal neuropathy *Truncal mononeuropathies *Mononeuropathy multiplex *Asymmetric lower-limb motor neuropathy (amyotrophy)

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***Features of small and large fiber neuropathy**

Small fiber neuropathy (A alpha and C fibers)	Large fiber neuropathy (A delta fibers)
Pain and paresthesia Autonomic signs and symptoms Temperature loss No weakness Normal deep tendon reflexes	Impaired vibration Loss of position sense Wasting and weakness of muscles Loss of deep tendon

***Symptoms and signs of diabetic neuropathy [4]**

Symptoms		Signs	
Somaticsymptoms	**Autonomicsymptoms**	**Motorsymptoms/sign**	
Small fiber neuropathy Paresthesia - burning, pricking, electrical sensations. More severe at night Large fiber neuropathy Numbness over feet, hands, or specific sites, sensations of swelling, cotton-wool-like sensation, or a feelingthatthelimbis"dead"or"asleep."The symptomsworsenatnightandhavea symmetricaldistribution Pain sharpordeepburningpain withhyperesthesiaorallodynia	Cardiovascular Dizzinessongettingup,tachycardia, exerciseintolerance, Heat intolerance Genito-urinary Incontinenceorsensationofpartial emptying,erectiledysfunction Gastrointestinal Nausea and bloating sensation of abdomen, diarrhea, constipation, fecal incontinence Sweating Symptoms of inappropriately increased sweating, areas of anhidrosis Metabolic Hypoglycemia unawareness, hypoglycemia unresponsiveness Pupils Argyll Robertson-type pupils	Wasting of muscles, especiallyinhandsandfeet, weakness of muscle groups Loss of deep tendon reflexes	Sensoryloss (touch and temperature) Partial or complete Loss of vibration sense especially in the extremities

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*SOMATIC SENSORY SYMPTOMS

The most common type is symmetric distal sensory polyneuropathy.It affects distal lower extremities and hands in a "glove and stocking" pattern[**Figure 1**]. Symptoms of large fiber neuropathy (A-delta fibers) include a burning or tingling sensation in the feet or legs, a feeling of pressure, or a band wrapping around the feet and ankles. Nighttime is when the patient is most likely to have feelings of unsteadiness and gait instability. Burning or stabbing paraesthesia, which is worse at night, is the result of small fiber neuropathy (A alpha and C fibers), which is

less common.

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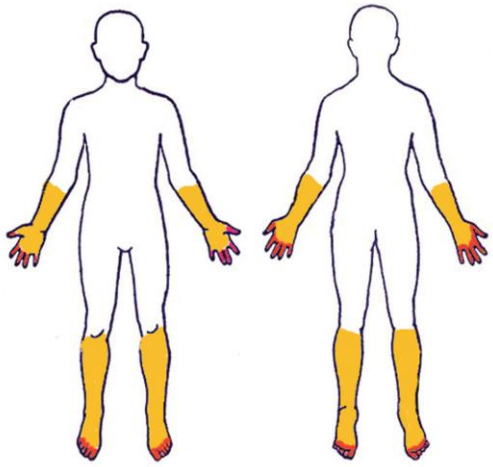

Figure 1: "Glove and stocking" neuropathy.

*AUTONOMIC SYMPTOMS

A high prevalence of autonomic neuropathy among people with diabetes (50%–60%) is related to significant mortality and morbidity. Cardiac autonomic neuropathy can, in specific, contribute to 6% of sudden deaths (painlessmyocardial infarction) out of those with long-standing diabetes. It is imperative, therefore, to put questions to obtain a history of autonomic dysfunction and perform proper investigations. Some of the simple questions that can reveal a hidden underlying autonomic neuropathy are:

• Gastroparesis- Do you feel full after eating less than you routinely eat?
• Cardiac autonomic neuropathy Do you experience vertigo after rising from a supine position (orthostatic hypotension)? Check for tachycardia at rest.
• Cystopathy- Decreased/increased urinary frequency and sensation of incomplete voiding after passing urine
• Gustatory sweating -Is there sweating over the face while eating?
• Erectile dysfunction.

PATHOGENESIS:

The pathogeneticmechanism of microvascular& macrovascular injuryis different. Various studies have deduced that hyperglycemia isthe main reason behind microvascular injury, whereas insulin resistance is themajor cause of macrovascular injury. The pathological changes following a macrovascular injury include atherosclerosis of arteries[5].

Mechanism of Microvascular complications:

Microvascular injury mainly involves cells like endothelial cells & mesangial cells [6]. Even though they are exposed to high concentrations of glucose via an efficient transport system, the

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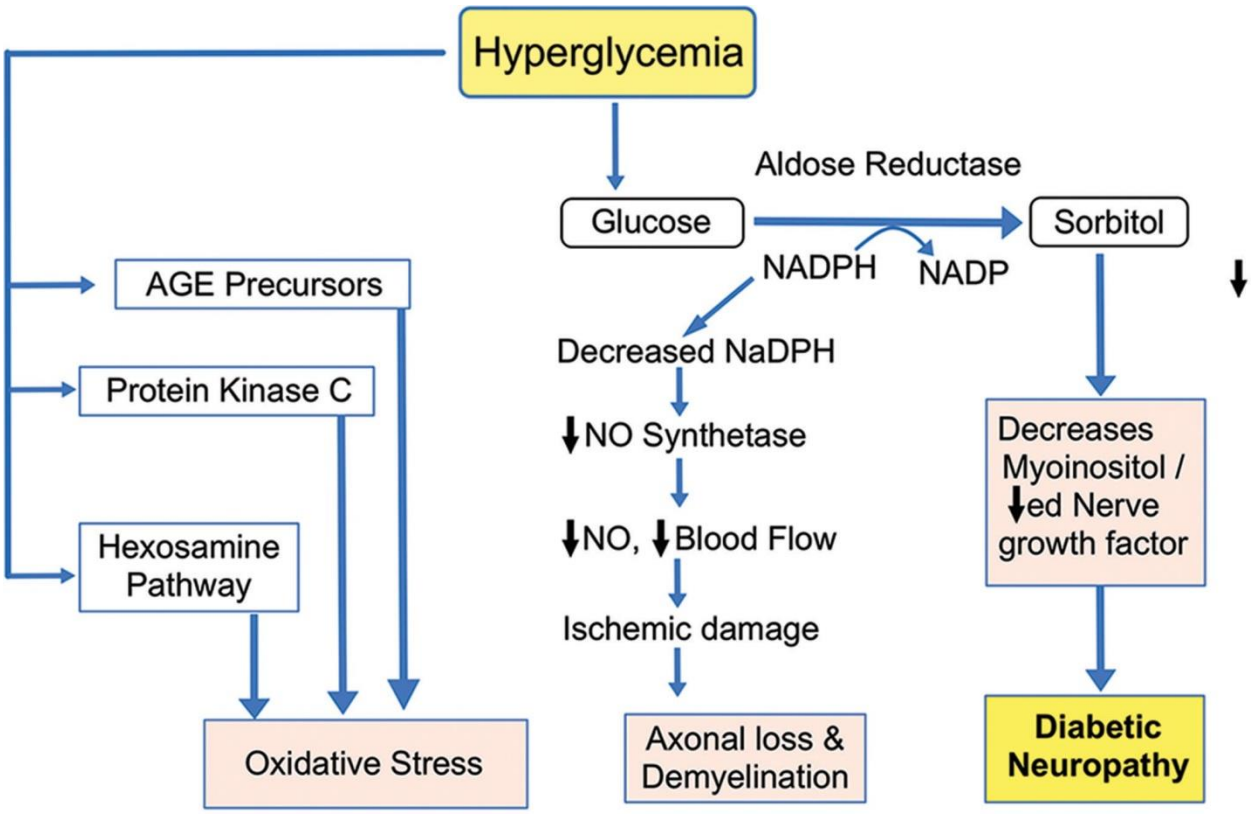
majority of our cells are capable of maintaining a constant internal glucose concentration. In contrast, the cells damaged by hyperglycemialose this potential & are exposed to the unfavorable effects of highglucose.

High glucose levels result in the accumulation of advanced glycosylated end products and the activation of other pathways, ultimately resulting in oxidative stress, axonal degeneration, and demyelination, which cause nerve dysfunction. Excess glucose also gets transformed into sorbitol by the enzyme aldose reductase. Sorbitol reduces myoinositol nerve growth factor levels, leading to diabetic neuropathy [Figure 2].Ideal glucose control is, therefore, the primary preventivemeasure.



[Figuer2]: Pathogenesis of Diabetic Neuropathy.

SCREENING TEST TO EVALUATE PERIPHERAL NEUROPATHY

1. Inspection of the feet and the footwear
2. To check Small fiber function:Pinprick test and temperature test
3. TO check Large fiber function: Vibration perception, monofilament test, and ankle reflexes
4. Protective sensation loss test: monofilament test

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5. Assessment OfMusculoskeletal deformity.
6. Vascular assessment of the feet
7. Examination of the footwear used, mainly at ulcer sites.

***Assessment of diabetic neuropathy**

A quantification or objective measurement of diabetic neuropathy can help evaluate progression/worsening andtreatment response.

***Monofilament test**

- It is possible to evaluate using standard-thickness SemmesWeinstein Monofilament single-fiber nylon threads. Commonly used ones are the 2 g (purple), 4 g (red), and 10 g (from thin to thick) (orange). The figure depicts the ten areas of the foot that are evaluated. (9 on the plantar aspect and one on the dorsal aspect)

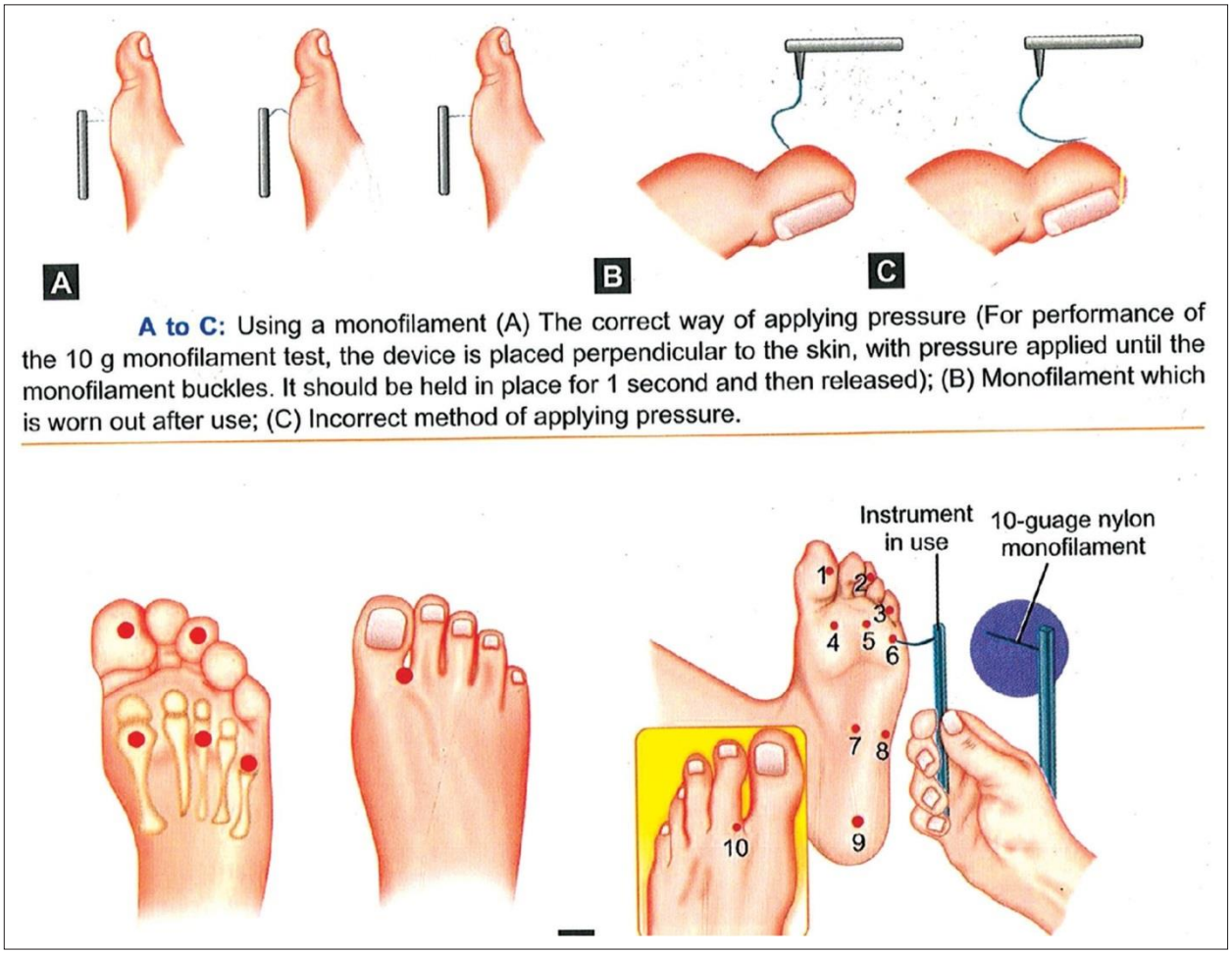

Fig: 3: 10g SEMMES WEINSTEIN MONOFILAMENT

***VIBRATION SENSE TEST**

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1)TUNNING FORK TEST 2)VIBRATION PERCEPTION BY BIOTHESIOMETER.

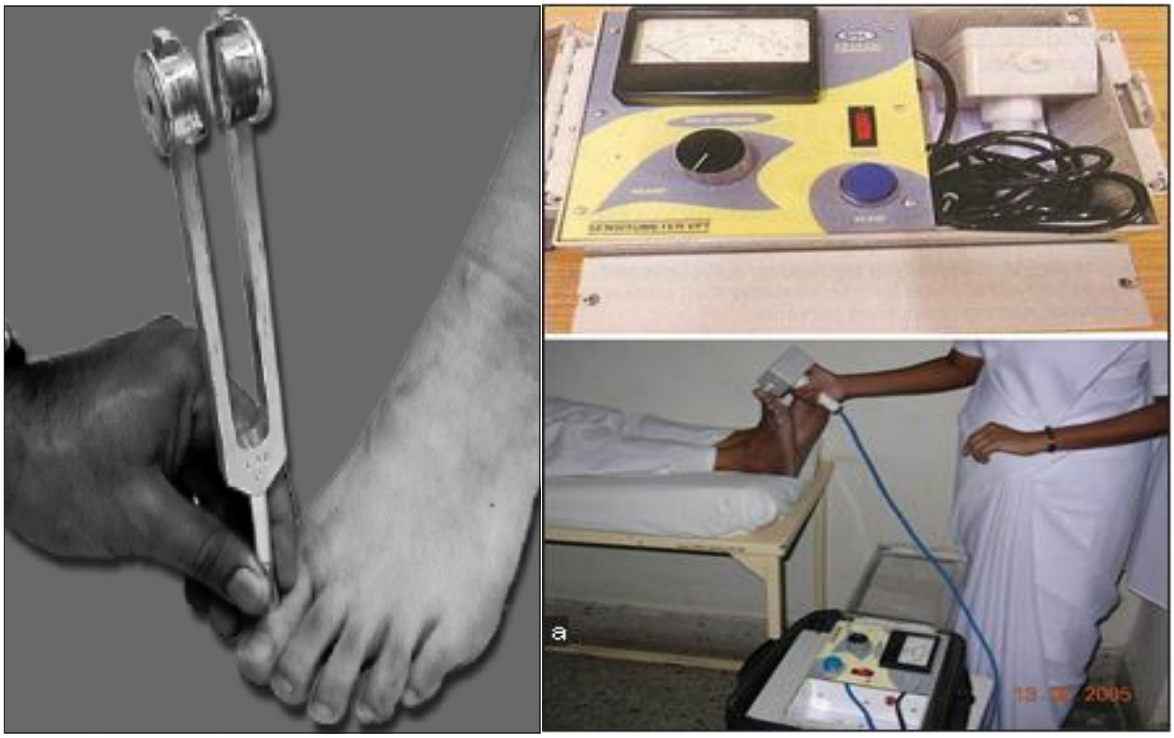

Figure4:Tuningforktestforvibrationsense.(b)Using a biothesiometer.Figure 5 :(a) Biothesiometer.

***Deep tendon reflexes**:In Typical Neuropathy Ankle Reflex Vanish First Followed by Knee Reflex.

***Motor function:**Weakness detected in toe extensors followed then toe flexors. As the neuropathy progress to the knee, patients develop weakness of the hand. Commonly the weakness beginsin dorsal and ventral interossei muscles and abductor digit minimi in the lower limbs.

***Electrophysiological testing**: assist in evaluating patients for DSP by motor and sensory nerve conduction studies.

DPN is an essential base at the beginning of the pathophysiological pathway to foot ulceration and amputation. The type of fibers that are involved in DPN (motor and sensory)is determined by Electrophysiological testing, but it also gives a gross estimation of the period of the neuropathy, and it also gives an intuition into the prognosis[6].

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*** Nerve conduction studies contain:**

(I) Motor function assessment of the median, ulnar, tibial, and peroneal nerve.

(II) Sensory function of ulnar, median, radial, and sural nerve.

(III) Velocities are termed in meters/second and mV(mill volts) motor amplitudes.

(IV) Sensory amplitudes in (µV)microvolts.

***Importance of Nerve conduction studies (NCS):**

1) Benchmark for diagnosis of neuropathy

2) Intensity of nerve fiber loss is reflected in nerve amplitude

3) In diabetes type 2 patients, the abnormalities were noticed in 40 to 60 %.

4) Abnormality of NCS rises with the period of diabetes.

Motor nerve conduction study (MNCV) is an individual predictor inpatient of diabetes for the new foot ulcers. MNCV is a "benchmark" for distal symmetrical diabetic polyneuropathy assessment.

CURRENT GUIDELINES AND MANAGEMENT OF DIABETIC NEUROPATHY

1) STRICT GLYCEMIC CONTROL-The Diabetes Controls and Complications Trial (DCCT)revealed that strict control of blood glucose in diabetes type-1 patients lower the risk of DPN by 60%[7].Not so in the case of type-2 diabetes; various studieshave revealed that aggressive glucose control has an insignificant impact on patient risk for polyneuropathy[8].

A systemic review by Callaghan et al. did demonstrate that strict glycemic control slower the progression ofpolyneuropathy in patients with both type 1 and type 2 diabetes.Although, tight glycemic control also increased the risk of hypoglycemic episodes.[9]

2)SYMPTOMATIC AND PAIN-REDUCING TREATMENT-

Peripheral neuropathy is themost standard type of diabetic neuropathic pain, and its most frequent symptom is moderate to severe pain. International recommendations were provided by the American Academy of Neurology (AAN), Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG IASP), European Federation of Neurological Societies (EFNS), and the National Institute for Health and Care Excellence (NICE) all accept that the first-line agents for management are calcium channel a2-d ligands (gabapentin and pregabalin) and Tricyclic antidepressants that block the reuptake of both serotonin and noradrenaline. Few patients may have help from opioids or topical agents with transdermal lidocaine.

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A) FIRST-LINE THERAPY

TRICYCLIC ANTIDEPRESSANTS AND SELECTIVE SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS-

(TCA's)-consists

AMITRIPTYLINE, IMIPRAMINE(tertiary amines),

NORTRIPTYLINE, DESIPRAMINE(secondary amines).

It stops the noradrenaline and serotonin reuptake at the presynaptic neuron.

Another assumed mechanism of action by hampering the uptake of both Serotonin and noradrenaline reuptake inhibitors may contribute to their analgesic effect.

DULOXETINE –It can reduce DPN-related pain by inhibiting noradrenaline and serotonin reuptake.

VENLAFAXINE- is a potent serotonin reuptake inhibitor; at medium to high doses, it inhibits noradrenaline reuptake.

CALCIUM CHANNEL A2-D LIG: Gabapentin, Pregabalin

The pregabalin and gabapentin act on the A2-D l subunit of the presynaptic Ca++channel via a similar mechanism of action[10]; the effect is to reduce the release of the neurotransmitters, mostly noradrenaline and glutamate, and to some degree, substance P.

B) SECOND-LINE THERAPY

OPIOID ANALGESICS- The effective opioids used in treating neuropathic pain are OXYCODONE,MORPHINE, AND METHADONE.

In selected clinical situations, opioid analgesics can be preferred as first-linetreatment[12]. However, some guidelines appraise opioids as second or more freshly third-linetherapies because of their potential for abuse and safety profile.

TRAMADOLis a partial l-receptor agonist and a weak opioid that suppresses serotonin and noradrenaline reuptake.

C) THIRD-LINE THERAPY

TOPICAL MEDICATIONS-

LIDOCAINE-It has low systemic penetration and is combined with other analgesic agents. Lidocaine patches 5% work as peripheral analgesics.

D) OTHER TREATMENTS

ALPHA LIPOIC ACID-Alpha lipoic acid (ALA) is an agent that has antioxidant properties. Itdirectly reduces pain by decreasing oxidative stress, a crucial mechanism in the pathogenesis of DPN pain.

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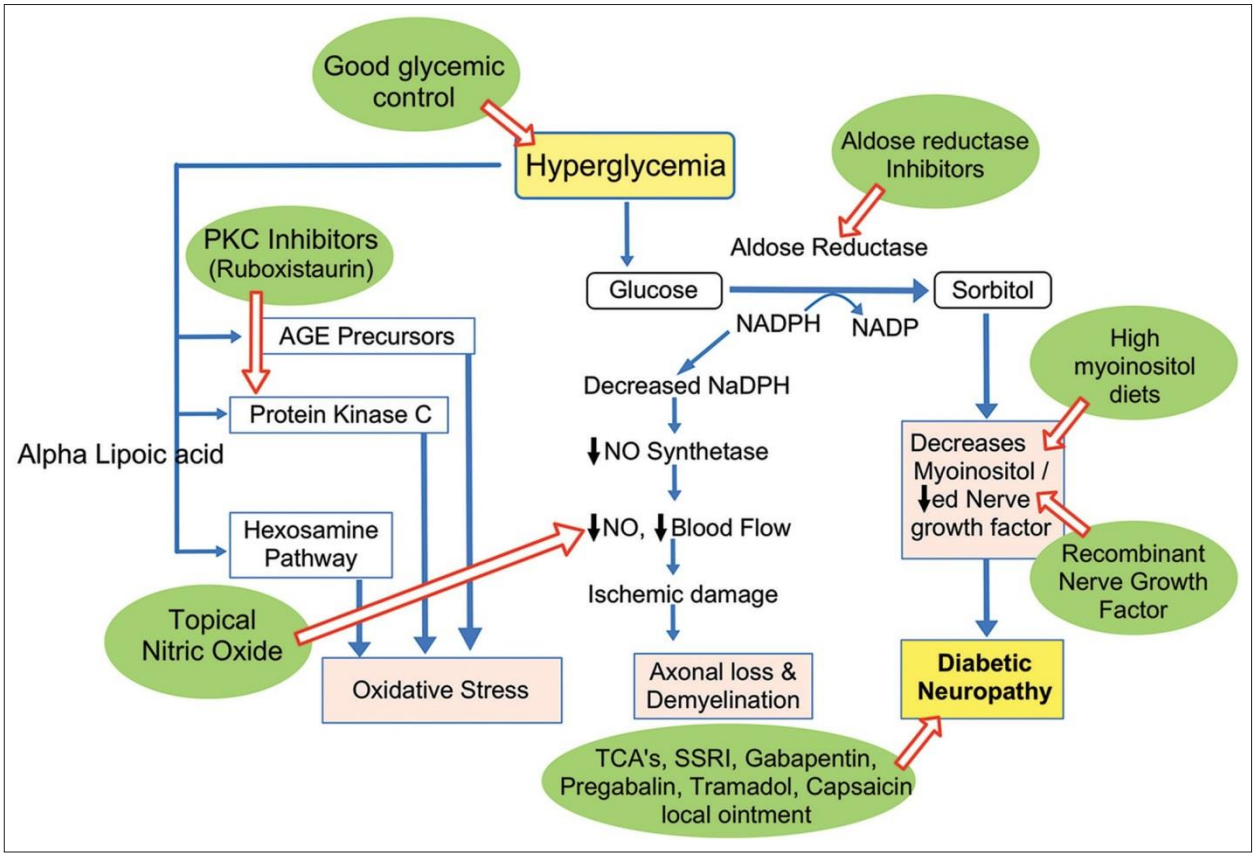

Figure 6:Agents used in the treatment of diabetic neuropathy.

CONCLUSION

•Peripheral Neuropathy is equally common in both diabetic &prediabetic individuals. It is more prevalent in elderly prediabetic individuals older than 70 years. Both males & females are equally affected; there is no sex predilection for the occurrence of peripheral neuropathy. Hypertensive individuals are affected more than non-hypertensives.

•There is a strong relationship between obesity & peripheral neuropathy in prediabetic individuals. The prevalence of dyslipidemia is higher in prediabetic people withperipheral neuropathy.

•There is emerging evidence that DPN in T2DM starts early & can even bepresent in pre-diabetes principally driven by vascular risk factors. There is evidence that risk factor management strategies can ameliorate DPN.
•All patients with type 2 diabetes should be screened for diabetic neuropathy from the beginning of diagnosis and five years after diagnosis of type 1 diabetes and at least yearly after that.

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• The clinical evaluation should contain a detailed history and 10 g monofilament testing and more than one of the following tests: vibration sensation test, pinprick test, and temperature test.
• Tight glucose control is the only best approach that has been demonstrated to show precaution and advancement of diabetic peripheral neuropathy and autonomic neuropathy.
• An annual thorough foot evaluation is a must for all patients with diabetes and consists of an examination of the foot and footwear, neuropathy screening, vascular assessment, and musculoskeletal assessment of the feet[4]. This would help in finding risk factors predictive of ulcers and amputation.

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