How to Cite:
Nair, D. K., Santhi, B., Simon, S. A., & Bupesh, G. (2022). Diabetic neuropathy and role of biochemical parameters in diabetic neuropathy: A narrative review. *International Journal of Health Sciences*, *6*(S4), 7123–7138. https://doi.org/10.53730/ijhs.v6nS4.10153

Diabetic neuropathy and role of biochemical parameters in diabetic neuropathy: A narrative review

Deepa K Nair
Bharath Institute of Higher Education and Research (BIHER), Selayur, Chennai, Tamilnadu, India & PMSCollege of Dental Science and Research,Vattappara, Trivandrum, India

B Santhi
Department of Biochemistry, Sree Balaji Medical College & Hospital, Chrompet, Chennai, Tamilnadu, India

Supriya A Simon
Department of Biochemistry, Government Medical College, Thrissur, Kerala, India

Giridharan Bupesh*
Department of Biochemistry, Sree Balaji Medical College & Hospital, Chrompet, Chennai, Tamilnadu, India & Department of Biochemistry, Government Medical College, Thrissur, Kerala, India & Natural Products and its Compound Research Laboratory, Department of Forest Science, Nagaland University, HQ: Lumami, Zunheboto - 798627, Nagaland, India
*Corresponding author

***Abstract*---**Diabetic neuropathy (DN) is the most widely recognized and distressing microvascular manifestation of diabetes, prompting the best degree of morbidity and mortality and bringing about an enormous financial weight for diabetes care. One of the major causesin DN is uncontrolled diabetes or hyperglycemia followed by nerve damage. The severity of DN is primarily associated with age, sex, plasma glucose level, hemoglobin A1C(HbA1C)value, length ofdiabetes, and Body Mass Index (BMI). The clinical assessment of peripheral neuropathy and its alternative treatments are multifactorial. The angiogenic proteinvascular endothelialgrowthfactor (VEGF) contributes a significant role in DN. Thus this review article presents knowledge about the different perspective soft hedisease, incidence epidemiology, pathophysiology, and the organ which are affected, diagnosis, prognosis followed by management of DN. The early diagnosis of diabetic neuropathies may help to reduce the severity of the disease as well the biochemical parameters involved in diabetic neuropathy

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 March 2022, Manuscript revised: 18 May 2022, Accepted for publication: 27 June 2022

can give a clear picture about the patient physical as well as the neurological status and protein like VEGF estimation can be used as a good predictor of Diabetic neuropathy.

***Keywords*---**diabetes mellitus (DM), hemoglobin A1C (HbA1C), diabetic neuropathy (DN), DPN,VEGF.

Introduction

Worldwide the metabolic disorder like Diabetes causes a significant health problem. Currently, complications of diabetes arewell known but the severity of diabetes-associated complications was vary depend on age, sex, plasma glucose level, HbA1C value, duration of diabetes, and body mass index. Four major complications are clinicallyproven in the case of DM; diabetic neuropathy, diabetic retinopathy (DR), diabetic nephropathy (DNe), anddiabeticvasculopathy (DV).The following ectionaimstoassessa systemic reviewof diabetic neuropathy and its contributing factorsespecially VEGF. It is confined by Ferrara and Davis-Smyth in 1989, is an intense endothelial cell mitogen that advances the expansion of vascular endothelial cellsand it has animportantroleinangiogenesis.[1–4]

Epidemiology of Diabetes Neuropathy

In India, the epidemiological studies were conducted in various parts ofruralandurbanareas, concludedthat there wasanincreaseintherateofincidence was notedinurbanareaswhencomparedtoruralareas. Many studies show a predominance of Diabetic peripheral neuropathy (DPN) was found to be 39.3% this is high compared to various polls in India, which are 19.1% and 29.2%.[5–7] As per 'The Foundation for Peripheral Neuropathy' 70% of the diabetics have perivascular neuropathy, 40% of malignancy patients having chemotherapy-associated peripheral neuropathy, and 30% of HIV/AIDS patients experience the ill effects of peripheral neuropathy. Their most recent findings reveal that 30 million Americans experience the adverse effects of certain kinds of DPN. Today, it is assessed that 60-70% of diabetics have DPN.[8] Diabetic neuropathic pathogenesis has not been effectively captured but tends to be a multifactorial problem, the result of congenital weakness, normal features, and lifestyle. The link between VEGF and diabetic neuropathy has received a lot of attention in recent years. The angiogenic cytokine VEGF is induced by hypoxia, improves tight permeability, supports the extracellular matrix, and promotes endothelial cell proliferation and hypertrophy[9]. However, VEGF has a negative effect on the vascular accumulation membrane, expands endometrial vascular permeability, causes ischemia and hypoxia of nerve fibers, and leads to the progression of neuropathy along with these effects.[10]According to Anjana et. al,the incidence of diabetes in the top 15 major states of India is 7·3% and the general predominance of prediabetes in each of the 15 regions was 10·3%[11].

Genetics

Type 2 diabetes is polygenic, with thousands of germline genetic loci thought to have a role in the disease, including more than 200 discovered so far.[12,13] Diabetic neuropathy is linked to several genes, however, only Angiotensinconvertingenzyme (ACE) andMethylene tetrahydrofolatereductase (MTHFR) encoding polymorphisms have been concentrated in different groups including enormous associates.[14]In a study which is related tothe genetics of neuropathy the researchers identified that one locus for neuropathy (rs78977169 near NRP2) showedgenome-wide significance in type 2 diabetes with diabetic neuropathy. NRP2 encodes neuropilin 2,a basal cell surface receptor engaged with VEGF-based angiogenesis and sensory nerve recovery.[15]The phenotypes such as ACE, AKR1B1, ADRA2B, APOE, GPx-1, IL-4, IL-10, IFN-γ, MTHFR, NOS1AP, NOS3, TLR4, UCP2, and VEGF shows a huge relationship with diabetic neuropathies in T2DM.[16]

Classification

'DN' (neuro-implies nerves; - pathy implies distress or enduring) is a kind of nerve injury that can happen in diabetics. The American Diabetes Association (ADA), diabetic neuropathy is the most common ongoing result of diabetes, the endocrine dysfunction[17]and, as per the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) 60-70% of individuals with both types of diabetes.[18,19]DN is mainly classified by NIDDK,anda comprehensiveclassification byADA.According toNIDDK there are four kinds of DN and area. Diabetic nerve pain and distal polyneuropathy or DPN, b. Diabetic amyotrophy or Proximal neuropathy, c. Autonomic Neuropathy, and d. Mononeuropathy or Focal neuropathy.

Diabetic PeripheralNeuropathy

Diabetic peripheral neuropathy might be a kind of nerve harm that normally influences the feet and legs and some of the time influences the hands and arms, this kind of neuropathy is quite normal. Dependent upon one-half of people with diabetes has DPN.[17,20] Themajor causeofperipheralneuropathiesis after prolonged elevations of plasma glucose, and increased degrees of fats like fatty oils, in the blood from diabetes can harm the nerves and the little veins that nourish the nerves, prompting peripheral neuropathy.Furthermore, the principle side effects are feeling unwell, shivering, similar to "a tingling sensation", numb, agonizing, pain in feet, legs, hands, and arms, in any event, when they are contacted with carelessness and the malfunction of the foot up that lead to abrasions and injuries. It can likewise make changes in the state of the feet and toes because of nerve injury.An uncommon condition that can happen in certain individuals with diabetes is Charcot's foot, an issue where the bones and tissue in the foot are harmed. DPN can make bound to loss of body equilibrium and fall, which can expand the opportunity of breaks and different wounds. The persistent aggravation of DPN likewise can cause depression, anxiety, and despair. The finding of DPN is dependent on side effects, family and clinical history, a clinical examination, and other diagnostic procedures. A neurological test, a foot test, and a blood test to examine for thyroid problems, kidney disorders, or decreased vitamin B12 levels are all important for an examination. Management and good

hyperglycemia control can tend to prevent DPN, and the suggested pain relievers along with physical rehabilitation to enhance stability and strength can aid with nerve pain treatment.[18]

Diabetic Proximal Neuropathy

This type of neuropathy also called diabetic amyotrophy or diabetic polyradiculopathy it is an uncommon and severe sort of nerve injury in the hip area, butt cheek, or thigh area. This sort of nerve harm by and large influences one part of the body and may seldom spread to the contrary side and are normal in men than in the female population and particularly individuals more established than age 50 with T2DM. The reasons for proximal neuropathy are the same as that of peripheral neuropathy yet the indications might remember unexpected and now and then extreme agony for hip, butt cheek, or thigh, hard to remain from a sitting situation because of the shortcoming of legs, loss of reflexes, and muscle tissue, weight reduction. Doing nerve conduction studies (NCV) and electromyography (EMG) can analyze proximal neuropathy. NCV is intended to check how quickly electrical impulses travel through nerves in various regions of the body. EMG measures how the muscle cells react to the neural impulses. The medicine used in DPN can also use to treat proximal neuropathy.[18]

Diabetic Autonomic Neuropathy (DAN)

DAN is harmful to nerves that control the body's internal organs. It can prompt issues with pulse and circulatory strain, digestion, bladder, sex organs, sweat glands, eyes, capacity to detect hypoglycemia.The excessive plasma glucose and fats, consisting of triglycerides, withinside the blood cells from diabetes can harm the nerve cells and the proximal veins that feed the nerves, principle to autonomic neuropathy. The symptoms depend on which body’s functions are affected and involved. The diagnosis is dependent on the indications, family and clinical history, as well as tests that are performed to assess the progressions in the pulse in light of profound breathing or standing and treatment by dealing with diabetes, circulatory strain, and cholesterol.[18]

Diabetic Focal Neuropathy

Focalneuropathiesormononeuropathyareconditions in which regularly have harm to single nerves, frequently in hand, head, torso, or leg and it is less common than DPN or DAN. In case of people who have diabetes can affect the different type of focal neuropathy and the most common type is entrapments or entrapment syndromes. It happens among bones and tissue, when nerves become packed or caught in regions where nerves go through restricted sections. Diabetes people are bound to have more complications than individuals without diabetes.[17]Carpal Tunnel disorder is the most well-known neuromuscular condition. Different sorts of focal that don't include caught nerves are more uncommon and regularly impact more seasoned adults. The most common type is cranial neuropathies, which influence the nerves of the head is one of the causes of focal neuropathy and it can cause issues with the eye or Bell's palsy, issues with the muscles of the face. Manifestations might shift depends upon which

nerve is influenced. Thesesorts of neuropathies that don't include caught nerves cause indications and it starts abruptly and works on following a little while or months. Contingent upon which nerve is influenced, individuals might have discomfort and different indications close by, leg, foot, and torso.Diagnosis and the treatment of focalneuropathyare the sameas proximalneuropathy.[18]

Pathogenesis

As per many investigations neuropathologically, the system of DN is difficult to explain with a single explanation, different speculations have been proposed. DN is separated into metabolic, vascular, and neuroregeneration theories of disease.[21–23]Diabetic neuropathy isn't considered fundamentally a demyelinating neuropathy many potential pathogenesis are involved in DN pathway like polyol pathway activation, intracellular myoinositol down-regulation, protein kinase C dysfunction, cAMP-down-regulation, Na+/K+/ATPase inhibition, nitric oxide degradation, protein glycation, free radical accumulation, impaired polyunsaturated unsaturated fat synthesis, irregularity in prostaglandin production, diminished nerve growth factor, debasement of Nerve blood circulation, and more severe nerve vascular obstruction.[24]

Organs implicated in diabetic neuropathy

Dependsupontheseverity,Diabetic neuropathy can influence the heart, lungs, veins, bone, fat tissue, sweat glands, gastrointestinal framework, and genitourinary framework. ComplicationsofDNcanbeworsenedif it is notcontrolled whichleadstodamagetothe nerve fibersresultingthe abnormalitiesinthe organ function.

Risk factors of Diabetic Peripheral Neuropathy

There are typically four traditional danger factors for DPN: hypertension, increased HbA1c level, hyperlipidemia, increasedtriglyceridelevel,andlowHDL cholesterol[18] also, the autonomous danger factors for the progression of diabetic neuropathy incorporate smoking, liquor misuse, aging, and larger stature.[14]Apart from the routinerisk factors which lead to DPN the risk like immune system disorders like GB disease(Guillain-Barre) & CIPD or Demyelinating Polyneuropathy are common risk factors affectingthe older adult. Autoimmune disorders like Celiac disease, Systemic lupus,Rheumatoid arthritis,Shingles as well asStress, Alcohol abuse, Vitamin deficiency especially vitamin B1 & B12,toxic substances include heavy metals, such as lead, mercury, arsenic, and organic solvents exposures; and certain medicinesused in cancer or AIDS treatment are the most common risk which leads to DPN according to "Thefoundation for PeripheralNeuropathy.[8]The major complications in diabetic neuropathies are unawareness of low plasma glucose level, Loss of a foot, leg, or a toe, infection in the urinary tract and urinary incontinence, sudden falls in bloodpressure,digestive systemproblems,and sexualdysfunction.[25]

Biochemical parameters involved in different types of DNs
Role of Aldose Reductase Activity in Diabetic autonomic neuropathy

The first rate-limiting intracellular enzyme, Aldose Reductase (AR) is in the polyol pathway, with the help of cofactor nicotinamideadeninedinucleotidephosphate(NADPH) reduces glucose to sorbitol.Theenzymesorbitoldehydrogenase is used for the metabolism of sorbitol to fructose.[26] Increased activation of aldose reductaseinduces the activation of polyol pathway which leads to the occurrence of diabetic microvascular complicationswhichincluderiskcardiovasculargeneration.BecauseoftheARactivityth elevelofsorbitol,theendproductofthepolyolpathwaywouldincreasesimultaneouslythe NADPHlevelwouldreduce,andfinallyitcausesoxidativestress to the cells and generation of free radicles followed by cell death[23,27]. Or cell damage. Estimation of RBCaldolase reductase activity is the one of clinical tools for the early prognosis of diabetic autonomic neuropathy.Many experiments have been proved the same. Example as indicated by Pawan Gupta et.al, investigation of with diabetes patients they had chosen complete of 177 subjects in that 145 subjects were with DAN or without DAN in addition to 32 without diabetes mellitus. The researchers concluded that people with diabetes mellitus and autonomic neuropathy had a significantly higher concentration of RBC aldose reductase activity than people with diabetes mellitus without autonomic neuropathy or healthy persons without diabetes mellitus.[28]

Role of Free radicals

The reactive oxygen species (ROS) and Reactive nitrogen species (RNS) are in contrast extremely unsound species that are free radicals or extreme elements that are both beneficial and destructive to the cell. Free radicals such as superoxide (O2), hydroxyl (HO), peroxyl (RO2 *), and hydroperoxyl (HRO2 *) are ROS, as well as nonradical species, for example, hydrogen peroxide (H2O2) and hydrochlorous acid (HOCl). RNS include radical species like nitric oxide (NO) and nitrogen dioxide (NO2) as well as nonradical species like peroxynitrite (ONOO), nitrous oxide (HNO2), and alkyl peroxynitrates (RONOO).[29](Figure2).

Role of Protein Kinase -C(PKC)

Serine/Threonine kinase group of protein kinase C (PKC) activated by diacyl glycerol, Many studiesconcluded that the action of diacyl glycerol and PKC has been increased in case of patients having diabetes andincaseofPKChasmultiplefunctionsinthecellandareinvolvedincontrollingtheVEG F, smooth muscle constriction, haemodynamics and endothelial cell penetrability and multiplication throughthe phosphorylationofhydroxylgrouppresentinthePKC and regulationofcellcycle.[29]

Roleof Cytokines and endothelial growth factors

Granulocyte-macrophage colony-stimulating factor (GM-CSF), platelet-derived growth factor (PDGF), vascular endothelial development factor (VEGF), and basic fibroblast growth factor (BFGF) are the four development factors, hepatocyte growth factor (HGF) and cytokines at present being utilized here and there name

for the regenerative healing of wounds in the event of diabetic neuropathy. HGF assumes significant parts in Schwann cell-intervened nerve regeneration, and such kind of gene exchange might give a helpful technique to treating DPN.Oncostatin M is an individual from the IL6 group of cytokines which is directed in many cells of the CNS. It is an amazing neuroprotective cytokine that forestalls the expression of the N-methyl-D-aspartate receptor, which contributes significantly to neuropathic nerve pain.[30,31]

Role Routine biochemical parameters-Plasma Glucose, HbA1C, Urine Microalbumin, EGFR

Accordingto ADA guidelines the role of routine biochemical parameterslike Blood Sugar, HbA1C, Microalbumin,and EGFR has provided a good clinical significance for the identification of diabetic neuropathy and its clinicalcomplications. The primary aim of these tests is to confirm the present diabetic status and help to interpret anddifferentiatewhichtypeofdiabeticneuropathyareaffected.[17]While considering the association between these parameters and the prevalence of DN many research studies areproof that there is a positive correlation between these parameters and clinically significant irrespective of ageandsex.Atthesametime,thestudiesshowthattheroleofbodymassindexindiabetesp ersonwhencompareto normal subjects to have a positive association and which is directly proportional to the complication or theseverity ofdiabetes-associatedneuropathy. Yet an investigation by Sangeetha Meena et.al, inferred that there was no huge relationship between DPN and different determinants like sex, term of diabetes, and BMI and they finished up the investigation the predominance of DPN among diabetic patients is over 40%. Age more than 50 and poor glycemic control were observed to be the fundamental determinants of DPN.[32]

Roleof25-hydroxyvitamin D (25(OH)D)

25-hydroxyvitamin D (25(OH)D) “Sun-Shine Vitamin” is also known as a multifunctional adrenocorticotropic hormone. Researches provethatthereisarelevantroleof serum25-hydroxyvitaminDindiabetessubjectsbecausevitamin Dassistsintheenhancementof the body' sinsulin sensitivity. Lower the concentration of vitamin Dinbloodstreamreduces the proper functioning of Insulin receptors and leads to insufficiency of insulin in the body, the majorhormone for regulating blood glucose levels. Imbalance in this mechanism leads to diabetes followed by DPN. Ina study by Alvarezet.al, vitamin D supplementation can boost glucose tolerance in people with T2DM byincreasing serum calcium, Reducing the amount of unsaturated fat in the bloodstream, improving insulin release, and whichimproves glucose tolerance.[33] According to Putz Z et al, study hypothesis, vitamin D deficiency is a significant cause of diabetic foot ulcers, one significant side effect of DN.[34]

Role of serum Phosphorousand Magnesium

Magnesium (Mg) is an intracellular cation or is an electrolyte in the human body. Magnesium in cells serves as a cofactor for various enzymes associated with

glucose transport, glucose oxidation, insulin secretion, additional serves as a cofactor for ATPase and enzymes that activate Adenylate Cyclase.[35]The main sources of Mg shortfalls in T2DM have diminished Mg consumption and additionally increased urinary Mg excretion, even though Mg assimilation and maintenance are normally maintained.[36] Mg likewise is profoundly associated with the insulin-stimulating pathway, in the phosphorylation of insulin receptor kinase, in a post-receptor role for insulin, and in insulin-intervened in cellular glucose absorption. Lacks of Mg status including both hypomagnesemia as well as diminished dietary Mg consumption have been connected to an increase in the risk of diabetes or metabolic syndrome. In contrast, higher Mg admissions were associated with a decreased incidence of T2DM.[37] A backward relationship exists between serum magnesium and fasting glucose or glycated hemoglobin levels.[38] Neuropathic pain and functional impairment following injury to the spinal cord are often improved by magnesium treatment.[39] Furthermore, low-level laser treatment enhanced the effects of DPN by enhancing serum magnesium levels.[40] Several studies concluded that lower levels of serum phosphate and magnesium together induced nerve conduction boundaries in T2DM patients. The pathophysiological aspects of DPN may be affected by the serum phosphate and magnesium levels.[41]

Role of VEGF

An endothelial-derived mitogen, VEGF is freed from the endothelial covering of the veins because of tissue ischemia in various parts of the body. This is the predominant factor in new vascular development or neovascularization.[42]Available for use a critical degree of heritability has been found to influence VEGF levels, up to 60−80%, of which half are dictated by its SNPs rs6921438 and rs10738760. However, a few investigations recommend that upregulation of VEGF might satisfy a defensive and neurotropic capacity, and VEGF-mediated mechanisms might work on diabetic neuropathy. Different studies show that a rise in circulating VEGF levels is associated with obsessive angiogenesis and changes in vascular penetrability, contributing to cardiovascular and diabetic complications, nerve ischemia, and hypoxia.[16]

Diagnosis

Different testing techniques are used along with routine biochemical tests such as fasting plasma glucose, HbA1C, unexpectedly elevated plasma glucose with side effects, and oral glucose tolerance test (OGTT), to distinguish the improvement of diabetic neuropathy. Depending upon the patient's[42]symptoms, medical history,andphysical examinationclinicallyDNdiagnosebychecking thelossofsensationtopinprick, temperature, vibration by vibrating tuning fork to the toe, and proprioception in a 'stocking and glove'distribution for small nerve fibers. Diabetic neuropathy can be evaluated through scales that have defined cut-off values, such as the Ontario Clinical Neuropathy Score,[43] the Toronto Clinical Neuropathy Score modified,[44]and/or the Michigan Diabetic Neuropathy Score [38].The following non-obtrusive electrodiagnostic tests are routine for diabetic neuropathy diagnosis.Nerve conduction studies(NCS), Electromyography (EMG), Quantitative Sensory Testing (QST), Nerve, Skin, Muscle, Tissue Biopsy, Lumbar Puncture test, and autonomictestingrecommendedforthedetection ofDN.

Prevention

The best method to prevent DN is by controlling the blood glucose level followed by managing diabetes andmaintaining the body mass index. Diabetic-related nerve damage can also prevent by following regularexercise, avoiding or limiting smoking and alcohol consumption, regularly monitoring the foot to preventulcerationandpropermedicationwithroutinemedicalcheck-ups.

Treatment

Diabetic neuropathy is a perpetual condition for which there is no data regarding the effectiveness of treatment plans designed to manage it permanently.[45]As indicated by NIDDK[18] prescriptions like antidepressants, anticonvulsants, and skin creams, fixes, or showers, for example, lidocaine can be used to treat diabetic nerve pain neuropathy and suggest different medicines for the pain, including exercise-based therapies to work on the strength and balance and bed support, an accessory that keeps sheets and covers off the legs and feet during sleep. The recent American Academy of Neurology(AAN)[45]examines show proof-based rule "Treatment of Painful Diabetic Neuropathy," there was lacking proof to help or invalidate the helpfulness of α-lipoic acid (ALA), in restorative mediations however presently ALA utilized for the treatment of DPN. Pregabalin is set up as viable and ought to be offered to patients suffering from symptoms of DPN (Level A). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, narcotics (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are most likely powerful and ought to be considered for treatment of DPN (Level B). The evidence isnegative or less robust in the case of other treatments. The availability of medications to treat DPN is good, however many have side effects that limit their utility, and few studies have provided adequate information about the effectiveness of treatment.Currently,manystudiesconcluded that pharmacologically first-line medicines such as pregabalin, gabapentin are used for DPN therapiesfollowedbygoodfoothygiene arerecommended.

A Current Assessment of Diabetic Neuropathy and its Future

In India, approximately more than 10 lakhs of cases were reported that people having diabetes mellitus withneuropathicnervedamage.Ethnic contrasts in microvascular activity in limbs in the South Asian patient's withT2DM contrasted with White Europeans. In this intriguing research, skin microvascular blood-stream evaluation exhibited decreased heated activity yet saved acetylcholine reaction in South Asians.The lower incidence of DPN among South Asians is likely to explain this.[46] According to Eva L. Feldman et al. and group, without any effective intervention, 33% of the normal 9.7 billion people will have diabetes and a large portion of them will have neuropathy as of 2050.[14] Recently Marlon Yovera-Aldana et al,an extended study and meta-study for each country in Latin America and the Caribbean population determined that DPN prevalence and occurrence were moderately high there compared with other geographic regions as practically 50% of diabetes patients now have DPN despite extremely limited evidence.[47] According to IDF 2019 Atlas shows inIn India 77.0 million people having diabetes when compared to other South-East Asian countries andthe study reveals that South-East Asia used USD 8.1 billion on diabetes-related

wellbeing, which was the second least amount of this kind of use in the global diabetes community and in 2045 theprevalence of diabetic will increase upto 12.0 billion with 1.3 billion of the adult population with diabetesand it is estimated that there will be an increase of 88 million to 153 million individuals with diabetes (74% higher).[48]Worldwide, 422 million people have diabetes, the majority of whom are living in low- and middle-income nations and 1.6 million deaths are directly traceable to diabetes each year according to World Health Organization statistics. There has been a steady increase in both diabetes mellitus cases and its widespreadness in the last few years.[49] National Diabetes Statistics Report of the Centers for Disease Control and Prevention (CDC), a pervasiveness study released in 2020 estimated that there were 34.2 million Americans with diabetes or 10% of the adult population of the United States. One-fifth does not realize they have it. In fact, diabetes is the seventh leading cause of death in the United States.[50] Patients with diabetes and neuropathy who keep a decent glycemic control, diabetes self-sustainable lifestyle, diet, and active work can increase personal satisfaction by staying away from diabetic distress (DD), in addition to this, 3D study results suggest that 45.4% of type 2 diabetic patients show driven diabetic distress--the invisible emotional burden of diabetes.[21,51]

Conclusion

In the current study, the DN was evaluated for its clinical relevance, as it is a prominent component of Diabetes Mellitus and a widespread entanglement. Ongoing studies are being carried out on the counteraction and management of diabetic neuropathy, as well as on minimizing neuropathic pain and its related complications.In addition, VEGF, and numerous other proteins complicate the diabetes neuropathic pathwayandcurrently,estimationof these proteins is having significance in a patient with long-term Diabetes. The prior estimation of VEGF mayhelp to control the Diabetic patients to minimize neuropathic complications. Many studies have proven that antioxidant therapy also can be suggested for the treatment of diabetic neuropathy because it can minimize thecomplicationsofneuropathicrelateddiabeticcomplications.

Acknowledgements
None

List of abbreviations

DM- Diabetes Mellitus
HbA1C -Hemoglobin A1C
DN- Diabetic neuropathy
DPN- Diabetic peripheralNeuropathy
VEGF-VascularEndothelialgrowthFactor

References

1. 2016 Foundation for Peripheral Neuropathy International Research Symposium: Advances in Neuropathy - Emerging Therapies. *J Peripher Nerv Syst* 2017; 00: 1–24.
2. Alvarez JA, Ashraf A. Role of Vitamin D in Insulin Secretion and Insulin

Sensitivity for Glucose Homeostasis. *Int J Endocrinol* 2010; 2010: 1–18.
3. Anand AV, Bharathi V, Bupesh G, et al. Identification of novel potent pancreatic lipase inhibitors from Ficus racemosa. *Biomedicine* 2021; 41: 23–30.
4. Anjana RM, Deepa M, Pradeepa R, et al. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol*. Epub ahead of print 2017. DOI: 10.1016/S2213-8587(17)30174-2.
5. Anju M, Chacko L, Chettupalli Y, et al. Effect of Low Level Laser Therapy on serum vitamin D and magnesium levels in patients with diabetic peripheral neuropathy – A pilot study. *Diabetes Metab Syndr Clin Res Rev* 2019; 13: 1087–1091.
6. Barbagallo M. Magnesium and type 2 diabetes. *World J Diabetes* 2015; 6: 1152.
7. Barrientos S, Brem H, Stojadinovic O, et al. Clinical application of growth factors and cytokines in wound healing. *Wound Repair Regen* 2014; 22: 569–78.
8. Bowser-Riley F, House CR. The actions of some putative neurotransmitters on the cockroach salivary gland. *J Exp Biol* 1976; 64: 665–76.
9. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011; 76: 1758–1765.
10. Bril V, Perkins BA. Validation of the Toronto Clinical Scoring System for diabetic polyneuropathy. *Diabetes Care* 2002; 25: 2048–52.
11. Bril V, Tomioka S, Buchanan RA, et al. Reliability and validity of the modified Toronto Clinical Neuropathy Score in diabetic sensorimotor polyneuropathy. *Diabet Med* 2009; 26: 240–246.
12. Darivemula S, Nagoor K, Patan SK, et al. Prevalence and Its Associated Determinants of Diabetic Peripheral Neuropathy (DPN) in Individuals Having Type-2 Diabetes Mellitus in Rural South India. *Indian J Community Med* 2019; 44: 88–91.
13. DHHS. National Diabetes Statistics Report, 2020. *Natl Diabetes Stat Rep*.
14. Farsi L, Naghib Zadeh M, Afshari K, et al. Effects of combining methylprednisolone with magnesium sulfate on neuropathic pain and functional recovery following spinal cord injury in male rats. *Acta Med Iran* 2015; 53: 149–57.
15. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Prim* 2019; 5: 41.
16. Fisher L, Hessler DM, Polonsky WH, et al. When is diabetes distress clinically meaningful?: establishing cut points for the Diabetes Distress Scale. *Diabetes Care* 2012; 35: 259–64.
17. Good to Know: Nerve Damage and Diabetes. *Clin Diabetes* 2019; 37: 391–392.
18. Günther T. Magnesium in bone and the magnesium load test. *Magnes Res* 2011; 24: 223–224.
19. Gupta P, Verma N, Bhattacharya S, et al. Association of Diabetic Autonomic Neuropathy with Red Blood Cell Aldose Reductase Activity. *Can J Diabetes* 2014; 38: 22–25.
20. Joy SS, George TP, Siddiqui K. Low magnesium level as an indicator of poor

glycemic control in type 2 diabetic patients with complications. *Diabetes Metab Syndr Clin Res Rev* 2019; 13: 1303–1307.
21. Kawano T. A Current Overview of Diabetic Neuropathy – Mechanisms, Symptoms, Diagnosis, and Treatment. In: *Peripheral Neuropathy*. InTech, 2014, pp. 1–105.
22. M. Nagarajan Meenakshi Sundaram, K and M. Sundararaman RR. Marine Biotechnology: Potentials of Marine Microbes and Algae with Reference to Pharmacological and Commercial Values. In: *Plant Biology and Biotechnology*. Springer New Delhi, 2015, p. pp-685.
23. Mahardika, I. M. R., Suyasa, I. G. P. D., Kamaryati, N. P., & Wulandari, S. K. (2021). Health literacy is strongest determinant on self-monitoring blood glucose (SMBG) type 2 DM patients during COVID-19 pandemic at public health centre in Tabanan Regency. *International Journal of Health & Medical Sciences*, *4*(3), 288-297. https://doi.org/10.31295/ijhms.v4n3.1752
24. Manivannan C, Meenakshi Sundaram K, Sundararaman M, et al. Investigation on the inclusion and toxicity of acriflavine with cyclodextrins: A spectroscopic approach. *Spectrochim Acta - Part A Mol Biomol Spectrosc* 2014; 122: 164–170.
25. Manivannan C, Saravanamoorthy S, Meenakshisundaram K. Investigation on the Intercalation and Toxicity of 9-Aminoacridine in Zinc/Aluminium Layered Double Hydroxide Nanocomposites with Controlled Release Properties. *J Bionanoscience* 2017; 11: 482–488.
26. Meena S, C. MR. Prevalence of peripheral neuropathy and peripheral artery disease in diabetic patients attending a tertiary care hospital. *Int J Adv Med* 2019; 6: 1493.
27. Nada WM, Abdel-Moety DA. Evaluation of Serum and Aqueous Humor Vascular Endothelial Growth Factor in Neovascular Glaucoma. *Open J Ophthalmol* 2017; 07: 79–87.
28. Nomair A, ElDeeb MK, Maharem D. Aldose reductase (-106) C/T gene polymorphism and possibility of macrovascular complications in Egyptian type 2 diabetic patients. *Indian J Endocrinol Metab* 2016; 20: 648.
29. Oyenihi AB, Ayeleso AO, Mukwevho E, et al. Antioxidant strategies in the management of diabetic neuropathy. *Biomed Res Int* 2015; 2015: 515042.
30. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; 40: 136–154.
31. Putz Z, Martos T, Németh N, et al. Vitamin D and neuropathy. *Orv Hetil* 2013; 154: 2012–2015.
32. Saravanan KM, Kannan M, Meera P, et al. E3 ligases: a potential multi-drug target for different types of cancers and neurological disorders. *Future Med Chem*. Epub ahead of print January 2022. DOI: 10.4155/fmc-2021-0157.
33. SARAVANAN KM, SUNDARAM KM. EFFECT OF BROMOCRIPTINE IN DIABETES MELLITUS: A REVIEW. *UTTAR PRADESH J Zool* 2021; 1166–1170.
34. Senthil R, Meenakshi Sundaram K, Bupesh G, et al. Identification of oxazolo[4,5-g]quinazolin-2(1H)-one derivatives as EGFR inhibitors for cancer prevention. *Asian Pacific J Cancer Prev*.
35. Sheehan JP. Magnesium deficiency and diabetes mellitus. *Magnes Trace Elem* 2002; 10: 215–9.
36. Shera AS, Jawad F, Maqsood A, et al. Prevalence of chronic complications and associated factors in type 2 diabetes. *J Pak Med Assoc* 2004; 54: 54–9.

37. Sundaram KKM, Bupesh G, Saravanan KM. Instrumentals behind embryo and cancer: a platform for prospective future in cancer research. *AIMS Mol Sci* 2022; 9: 25–45.
38. Sundararaman, M N, Maruthanayagam V, et al. Tropical Marine Cyanobacterium Lyngbya sordida Producing Toxic Octacosa–1,27-diene Induces Coagulative Hepatic Necrosis and Progressive Glomerulonephritis in Mus musculus. In: *Encyclopedia of Marine Biotechnology*. John Wiley & Sons Ltd, 2020, pp. 2339–2364.
39. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. *International Journal of Health Sciences*, *5*(1), i-v. https://doi.org/10.53730/ijhs.v5n1.2864
40. Tavakoli M, Gogas Yavuz D, Tahrani AA, et al. Diabetic Neuropathy: Current Status and Future Prospects. *J Diabetes Res* 2017; 2017: 5825971.
41. Tonali P. [Diabetic neuropathy]. *Minerva Med* 1976; 67: 270–9.
42. Udler MS. Type 2 Diabetes: Multiple Genes, Multiple Diseases. *Curr Diab Rep* 2019; 19: 55.
43. Vujkovic M, Keaton JM, Lynch JA, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat Genet* 2020; 52: 680–691.
44. WHO. Global health risks (2009). http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf. *World Heal Organ* 2009; 1–55.
45. Witzel I-I, Jelinek HF, Khalaf K, et al. Identifying Common Genetic Risk Factors of Diabetic Neuropathies. *Front Endocrinol (Lausanne)* 2015; 6: 1–10.
46. Yadav S, Ramesh V, Bhatia E, et al. A prospective study of prevalence and association of peripheral neuropathy in Indian patients with newly diagnosed type 2 diabetes mellitus. *J Postgrad Med* 2014; 60: 270.
47. Yovera-Aldana M, Velásquez-Rimachi V, Huerta-Rosario A, et al. Prevalence and incidence of diabetic peripheral neuropathy in Latin America and the Caribbean: A systematic review and meta-analysis. *PLoS One* 2021; 16: e0251642.
48. Zakin E, Abrams R, Simpson DM. Diabetic Neuropathy. *Semin Neurol* 2019; 39: 560–569.
49. Zhang Q, Ji L, Zheng H, et al. Low serum phosphate and magnesium levels are associated with peripheral neuropathy in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2018; 146: 1–7.
50. Zhang X, Sun Z, Jiang H, et al. Relationship between single nucleotide polymorphisms in the 3'-untranslated region of the vascular endothelial growth factor gene and susceptibility to diabetic peripheral neuropathy in China. *Arch Med Sci* 2014; 5: 1028–1034.
51. Ziegler D, Strom A, Bönhof GJ, et al. Deficits in systemic biomarkers of neuroinflammation and growth factors promoting nerve regeneration in patients with type 2 diabetes and polyneuropathy. *BMJ open diabetes Res care* 2019; 7: e000752.
52. Zitouni K, Tinworth L, Earle KA. Ethnic differences in the +405 and −460 vascular endothelial growth factor polymorphisms and peripheral neuropathy in patients with diabetes residing in a North London, community in the United Kingdom. *BMC Neurol* 2017; 17: 125.
53. Zochodne DW. Diabetic polyneuropathy: an update. *Curr Opin Neurol* 2008; 21: 527–33.

Figure 1. Diabetic Neuropathy mechanism.Components connected to T1DM shows in yellow tone, T2DM in blue, and both in green shading cause DNA mutations, endoplasmic reticulum dysfunction, mitochondrial deterioration, cell injury, and irreversible degeneration. The significance of this pathway's organization will change with cell type, disease profile, and time. Endoplasmic Reticulum -ER; Free fatty acids -FFA; Phosphatidylinositol-3 kinase -PI3-K;Reactivenitrogenspecies-RNS; Reactiveoxygenspecies-ROS.The figure has been adapted and redrawn from Callaghan et al. Lancet Neurol 2012;11(6):521-34.

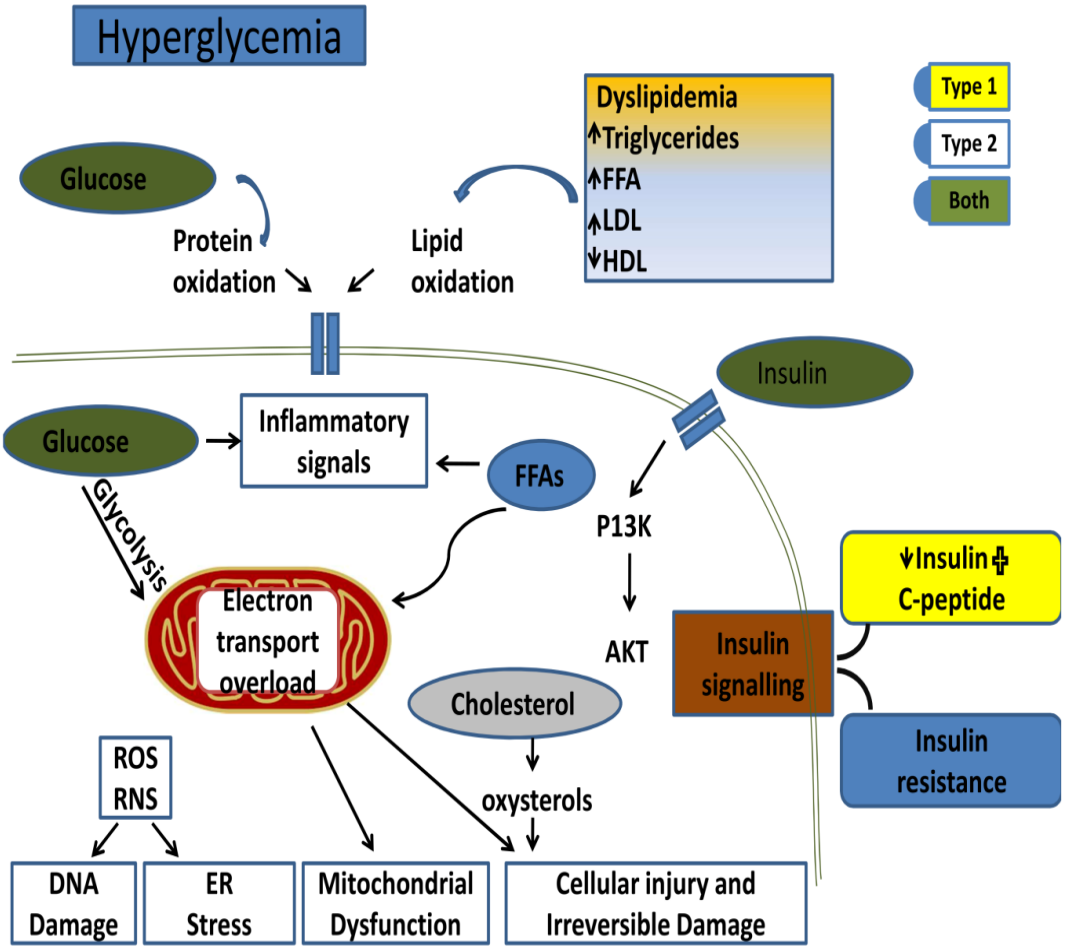

Figure2.Pathogenesis of DN.High plasma glucose and elevated lipid levels, as well as altered insulin signaling, lead to a couple of over-the-top changes in neurons, glia and vascular cells that can incite nerve brokenness and finally, neuropathy, including DNA damage, endoplasmic reticulum dysfunction, mitochondrial brokenness, neurodegeneration and loss of neurotrophic activity, and can trigger macrophage incitation. The meaning of these pathways in the improvement of neuropathy varies with cell type, the illness profile and time, as unquestionable cell types are practically defenseless against injury dependent upon the metabolic impedances. The figure has been adapted and redrawn from Bril et al. Diabet Med 2009; 26(3): 240-246.

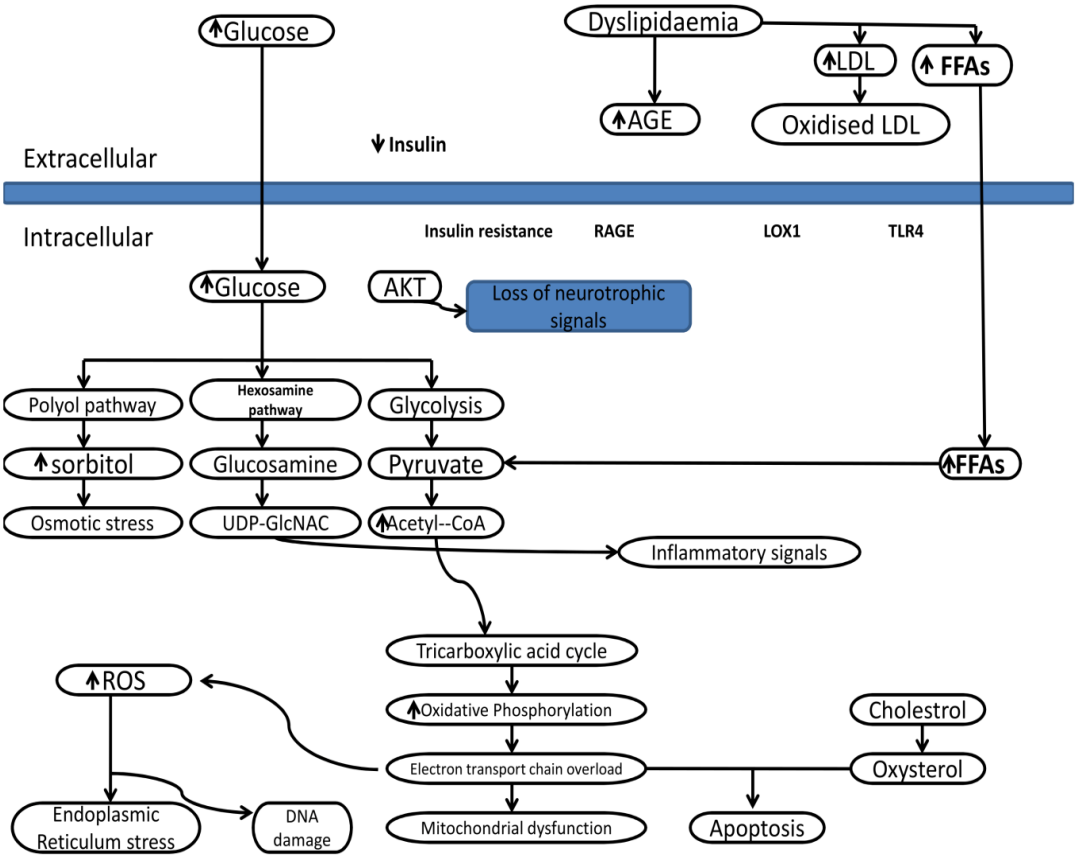

Figure 3. Biological and chemical agents that control diabetic neuropathy. Advancedglucoseend-products -AGEs;proteinkinaseC -PKC; poly-ADPribosepolymerase-PARP; aldosereductaseinhibitors-ARIs;reactiveoxygenspecies -ROS;reactivenitrogenspecies -RNS;superoxideradical -·O2; hydroxyl radical -·HO; peroxyl radical- ·RO2 ; hydroperoxyl radical -·HRO2 ; hydrogenperoxide -H2O2; hydrochlorous acid- HOCl; nitric oxide radical-·NO; nitrogen dioxide radical -·NO2; peroxynitrite- ONOO;nitrous oxide -HNO2;alkylperoxynitrates RONOO.The figure has been adapted and redrawn from Oyenihi et al. Biomed Res Int 2015: 515042.