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

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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 causes in 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 of diabetes, 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 of disease, 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 as the biochemical parameters involved in diabetic neuropathy.
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 are well 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 clinically proven in the case of DM; diabetic neuropathy, diabetic retinopathy (DR), diabetic nephropathy (DNe), and diabetic vasculopathy (DV). The following section aims to assess a systemic review of diabetic neuropathy and its contributing factors especially VEGF. It is confined by Ferrara and Davis-Smyth in 1989, is an intense endothelial cell mitogen that advances the expansion of vascular endothelial cells and it has an important role in angiogenesis.

**Epidemiology of Diabetes Neuropathy**

In India, the epidemiological studies were conducted in various parts of rural and urban areas, concluded that there was an increase in the rate of incidence was noted in urban areas when compared to rural areas. 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%, 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. 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. 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. 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%.
**Genetics**

Type 2 diabetes is polygenetic, with thousands of germline genetic loci thought to have a role in the disease, including more than 200 discovered so far.\textsuperscript{12,13} Diabetic neuropathy is linked to several genes, however, only Angiotensinconvertingenzyme (ACE) and Methylenetetrahydrofolatereductase (MTHFR) encoding polymorphisms have been concentrated in different groups including enormous associates.\textsuperscript{14} In a study which is related to the genetics of neuropathy the researchers identified that one locus for neuropathy (rs78977169 near NRP2) showed genome-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.\textsuperscript{15} The phenotypes such as ACE, AKR1B1, ADRA2B, APOE, GPx-1, IL-4, IL-10, IFN-\gamma, MTHFR, NOS1AP, NOS3, TLR4, UCP2, and VEGF shows a huge relationship with diabetic neuropathies in T2DM.\textsuperscript{16}

**Classification**

‘DN’ (neuro-implying 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\textsuperscript{17} and, as per the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) 60-70\% of individuals with both types of diabetes.\textsuperscript{18,19} DN is mainly classified by NIDDK, and a comprehensive classification by ADA. According to NIDDK 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 Peripheral Neuropathy**

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.\textsuperscript{17,20} The major cause of peripheral neuropathies is 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. These sorts 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 focal neuropathy are the same as proximal neuropathy.\textsuperscript{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.\textsuperscript{21–23} Diabetic neuropathy isn't considered fundamentally a demyelinating neuropathy many potential pathogenesis are involved in DN pathway like polyl 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.\textsuperscript{24}

Organs implicated in diabetic neuropathy

Depends upon the severity, Diabetic neuropathy can influence the heart, lungs, veins, bone, fat tissue, sweat glands, gastrointestinal framework, and genitourinary framework. Complications of DN can worsened if it is not controlled which lead to damage to the nerve fibers resulting the abnormalities in the organ function.

Risk factors of Diabetic Peripheral Neuropathy

There are typically four traditional danger factors for DPN: hypertension, increased HbA1c level, hyperlipidemia, increased triglyceride level, and low HDL cholesterol.\textsuperscript{18} Also, the autonomous danger factors for the progression of diabetic neuropathy incorporate smoking, liquor misuse, aging, and larger stature.\textsuperscript{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 affecting the older adult. Autoimmune disorders like Celiac disease, Systemic lupus, Rheumatoid arthritis, Shingles as well as Stress, Alcohol abuse, Vitamin deficiency especially vitamin B1 & B12, toxic substances include heavy metals, such as lead, mercury, arsenic, and organic solvents exposures; and certain medicines used in cancer or AIDS treatment are the most common risk which leads to DPN according to The foundation for Peripheral Neuropathy.\textsuperscript{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 blood pressure, digestive system problems, and sexual dysfunction.\textsuperscript{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 nicotinamide adenine dinucleotide phosphate (NADPH) reduces glucose to sorbitol. The enzyme sorbitol dehydrogenase is used for the metabolism of sorbitol to fructose. Increased activation of aldose reductase induces the activation of polyol pathway which leads to the occurrence of diabetic microvascular complications which include risk cardiovascular generation. Because of the AR activity the level of sorbitol, the end product of the polyol pathway would increase simultaneously the NADPH level would reduce, and finally it causes oxidative stress to the cells and generation of free radicals followed by cell death. Estimation of RBC aldolase 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.

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 (HOCI). 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 peroxy nitrates (RONOO−).

Role of Protein Kinase -C(PKC)

Serine/Thrreonine kinase group of protein kinase C (PKC) activated by diacyl glycerol, Many studies concluded that the action of diacyl glycerol and PKC has been increased in case of patients having diabetes and increase of PKChas multiple functions in the cell and are involved in controlling the VEGF, smooth muscle constriction, haemodynamics and endothelial cell penetrability and multiplication through the phosphorylation of hydroxyl group present in the PKC and regulation of cell cycle.

Role of 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.\textsuperscript{30,31}

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

According to ADA guidelines the role of routine biochemical parameters like Blood Sugar, HbA1C, Microalbumin, and EGFR has provided a good clinical significance for the identification of diabetic neuropathy and its clinical complications. The primary aim of these tests is to confirm the present diabetic status and help to interpret and differentiate which type of diabetic neuropathy are affected.\textsuperscript{17} While considering the association between these parameters and the prevalence of DN many research studies are proof that there is a positive correlation between these parameters and clinically significant irrespective of age and sex. At the same time, the studies show that the role of body mass index in diabetes patients when compared to normal subjects to have a positive association and which is directly proportional to the complication or the severity of diabetes-associated neuropathy. 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.\textsuperscript{32}

**Role of 25-hydroxyvitamin D (25(OH)D)**

25-hydroxyvitamin D (25(OH)D) “Sun-Shine Vitamin” is also known as a multifunctional adrenocorticotropic hormone. Researches prove that there is a relevant role of serum 25-hydroxyvitamin D in diabetes subjects because vitamin D assists in the enhancement of the body’s insulin sensitivity. Lower the concentration of vitamin D in bloodstream reduces the proper functioning of Insulin receptors and leads to insufficiency of insulin in the body, the major hormone for regulating blood glucose levels. Imbalance in this mechanism leads to diabetes followed by DPN. In a study by Alvarez et al., vitamin D supplementation can boost glucose tolerance in people with T2DM by increasing serum calcium, reducing the amount of unsaturated fat in the bloodstream, improving insulin release, and which improves glucose tolerance.\textsuperscript{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.\textsuperscript{34}

**Role of serum Phosphorous and 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{37} A backward relationship exists between serum magnesium and fasting glucose or glycated hemoglobin levels.\textsuperscript{38} Neuropathic pain and functional impairment following injury to the spinal cord are often improved by magnesium treatment.\textsuperscript{39} Furthermore, low-level laser treatment enhanced the effects of DPN by enhancing serum magnesium levels.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 symptoms, medical history, and physical examination, clinically DN diagnose by checking the loss of sensation to pinprick, 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,\textsuperscript{43} the Toronto Clinical Neuropathy Score modified,\textsuperscript{44} and/or the Michigan Diabetic Neuropathy Score.\textsuperscript{38} The following non-invasive 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 autonomic testing recommended for the detection of DN.
Prevention

The best method to prevent DN is by controlling the blood glucose level followed by managing diabetes and maintaining the body mass index. Diabetic-related nerve damage can also prevent by following regular exercise, avoiding or limiting smoking and alcohol consumption, regularly monitoring the foot to prevent ulceration and proper medication without routine medical check-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. As indicated by NIDDK 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) examines show proof-based rules “Treatment of Painful Diabetic Neuropathy,” there was lacking proof to help or invalidate the helpfulness of α-lipoic acid (ALA), in restorative medications 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 is negative 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, many studies concluded that pharmacologically first-line medicines such as pregabalin, gabapentin are used for DPN therapies followed by good foot hygiene are recommended.

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 with neuropathic nerve damage. Ethnic contrasts in microvascular activity in limbs in the South Asian patient’s with T2DM 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. 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. 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. According to IDF 2019 Atlas shows in India 77.0 million people having diabetes when compared to other South-East Asian countries and the 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 the prevalence of diabetic will increase up to 12.0 billion with 1.3 billion of the adult population with diabetes and it is estimated that there will be an increase of 88 million to 153 million individuals with diabetes (74% higher). 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. 

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. 

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.

**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 pathway and currently, estimation of these proteins is having significance in a patient with long-term Diabetes. The prior estimation of VEGF may help 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 the complications of neuropathic-related diabetic complications.

**Acknowledgements**

None

**List of abbreviations**

DM- Diabetes Mellitus
HbA1C -Hemoglobin A1C
DN- Diabetic neuropathy
DPN- Diabetic peripheral Neuropathy
VEGF-VascularEndothelial growth Factor

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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; Reactive nitrogen species -RNS; Reactive oxygen species -ROS. The figure has been adapted and redrawn from Callaghan et al. Lancet Neurol 2012;11(6):521-34.
Figure 2. 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; protein kinase C -PKC; poly-ADPribosepolymerase-PARP; aldoseductaseinhibitors-ARIs; reactiveoxygen species -ROS; reactivenitrogen species -RNS; superoxideradical -O2; hydroxy radical -HO; peroxyl radical -RO2; hydroperoxy radical -HRO2; hydrogen peroxide -H2O2; hydrochlorous acid -HCl; nitric oxide radical -NO; nitrogen dioxide radical -NO2; peroxynitrite -ONOO; nitrous oxide -HNO2; alklyperoxynitrates RONOO. The figure has been adapted and redrawn from Oyenihi et al. Biomed Res Int 2015: 515042.