The Review Of
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Ameliorative Role Of Antioxidants In Diabetic Neuropathic Pain

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ABSTRACT

Diabetic neuropathy, a prevalent complication of diabetes mellitus affecting up to 50% of patients worldwide, manifests as peripheral nerve damage leading to debilitating pain, numbness, and reduced quality of life. Hyperglycemia-induced oxidative stress and inflammation play central roles in its pathophysiology, exacerbating nerve dysfunction through free radical generation, mitochondrial impairment, and cytokine release. Current treatments, including antidepressants (e.g., duloxetine), gabapentinoids, and SNRIs, offer limited efficacy (relief in only ~30% of cases), with challenges such as adverse effects (e.g., somnolence, gastrointestinal issues) and poor adherence. This review explores the ameliorative potential of antioxidants, particularly vitamins C and E, in mitigating diabetic neuropathic pain (DNP). These agents neutralize reactive oxygen species, restore antioxidant defenses (e.g., glutathione regeneration), and modulate molecular pathways like NMDA receptor activity and PKC activation, thereby reducing inflammation and improving nerve conduction. Preclinical and clinical evidence, including randomized trials showing enhanced pain scores (e.g., VAS reductions) and quality-of-life improvements with vitamin C (200 mg/day) plus duloxetine or vitamin E (400–700 mg/day) supplementation, supports their adjunctive role. Synergistic effects of combined C and E vitamins further enhance neurotrophic support and glycemic control. Despite promising outcomes, long-term studies are needed to optimize dosing and integration with standard therapies. Antioxidants represent a cost-effective, safe strategy to address DNP's unmet needs, warranting inclusion in clinical guidelines.

Keywords: diabetic neuropathy; neuropathic pain; oxidative stress; antioxidants; vitamin C; vitamin E; inflammation; quality of life

INTRODUCTION

Diabetes is a long-term metabolic disease marked by blood sugar levels increases that may harm different organs and result in serious and perhaps fatal health issues. As per the International Diabetes Federation (IDF), 415 million adults aged 20 to 79 years were estimated to have diabetes mellitus in 2015. This condition is increasingly linked to severe and potentially fatal health complications, the most common being microvascular (retinopathy, nephropathy, and neuropathy) along with macrovascular (which increases the risk of cardiovascular diseases by two to four times).(1)

Types of Diabetes Mellitus

Based on its origin and clinical manifestation, diabetes mellitus is categorized into three types: diabetes type 1, diabetes type 2, and gestational diabetes mellitus (GDM). An autoimmune condition known as diabetes type 1 is brought on by the body attacking the cells of the organ known as the pancreas that processes insulin, which leaves the body with little or no insulin. Diabetes type 2 is the most prevalent kind of the disease, making up around 90% of cases. It is brought on by combined abnormalities in resistance to insulin and insulin production. GDM develops throughout pregnancy and is linked to difficulties for both the mother and the fetus.(1) Diabetic neuropathy, a prominent side effect of diabetes mellitus (DM) that occurs in 51% of individuals with both form type one and type two DM, is characterized by peripheral nerve dysfunction and damage. This disease, which presents with a range of symptoms from asymptomatic to severe neuropathic discomfort and numbness, increases risk of foot ulcers, lower limb amputation, along death. The etiology of diabetic neuropathy includes hyperglycemia, dyslipidemia, microvascular disease, oxidative stress, neuronal inflammation, with mitochondrial dysfunction. Long-term DM, increased blood pressure, smoking, poor glycaemic control, height, heavy alcohol use, as well as advanced age include risk factors for diabetic neuropathy. It is known to occur in variable proportions.(2)

Diabetic Neuropathy

Diabetic neuropathy is a nerve disease that often begins in the feet and gradually extends to other parts of the body. It causes tingling, numbness, discomfort, and weakness in those with diabetes.(3)

The illness might be shown either subclinical, with a vast array of anomalies affecting peripheral and autonomic function of nerve that are together anomalies only apparent via meticulous testing, or clinically, with a variety of distinct symptoms. Diabetic neuropathy, or nerve damage resulting with prolonged exposure to elevated blood sugar, is a typical side effect of diabetes mellitus. Approximately 50% of people with diabetes experience this, making it one of the most prevalent side effects of the disease.(6)

Classification of Diabetic Neuropathy

A collection of nerve conditions known as diabetic neuropathy is brought on by diabetes mellitus. Any nerve in the body may be impacted by these conditions, which can result in a variety of symptoms and consequences. Diabetic neuropathy must be classified to be understood as a whole and to inform the most effective treatment plans. This is a thorough description of how diabetic neuropathy is classified.

Classification Based on Nerves (9)

- **Peripheral Neuropathy**: This most common kind of diabetic neuropathy affects peripheral nerves, which is responsible to transmitting signals through the CNS to all of the humans body's other systems. Potential symptoms include tingling, numbness, burning, or pain in the hands, arms, legs, or feet.
- **Autonomic Neuropathy**: The autonomic nerve cells, which regulate digestion, heart rate, blood pressure and other involuntary body processes, are impacted by autonomic neuropathy. Diarrhoea, vomiting, nausea, constipation, diarrhea, sexual dysfunction, and trouble controlling body temperature are some of the possible symptoms.
- **Proximal Neuropathy**: This kind of neuropathy, which also goes by the name diabetic amyotrophy, affects the nerves that run in the legs, thighs, hips, and buttocks. In the afflicted regions, it may result in excruciating pain, weakness, and muscular atrophy.

Classification Based on Symptom(10)

- **Sensory Neuropathy**: Tingling, numbness, or discomfort in the extremities are the main symptoms of this kind, which mostly affects sensory nerves. Sensitivity to touch as well as temperature changes may be increased in patients.
- **Motor Neuropathy**: Muscular twitching, cramping, weakness, and coordination lack of are all consequences of motor neuropathy, which damages the neuron that regulate muscular action. Walking, fine motor abilities, and balance may all be affected.
- **Autonomic Neuropathy**: Abnormal sweating patterns, gastrointestinal disorders (such as intestinal paresis), genitourinary signs and symptoms, and cardiovascular difficulties (such as orthostatic hypotension) are indicators of autonomic nerve dysfunction.

Classification on the Basis of Onset (11-12)

- **Onset of Acute Neuropathy**: Certain instances present with an abrupt beginning, when symptoms arise quickly over a short period. This might be caused by metabolic abnormalities or uncontrolled hyperglycemia.
- **Chronic-Onset Neuropathy**: It begins slowly, worsens with duration, and is often associated with chronic hyperglycemia and long-term diabetes.
- **Neuropathy with a Subtle Onset**: Develops gradually, with minor symptoms first becoming apparent and then more so. Because of the steady deterioration, early diagnosis might be difficult.

Prevalence

Prevalence of Diabetic Neuropathy in India

According to various studies conducted in India, the prevalence rate of DNP is as follows: About 50% of all diabetic individuals have diabetic neuropathy, a frequent consequence of diabetes mellitus 1. In research done in Mangalore, India, it was shown that 32.2% of patient with DM for more than 5 years had diabetic DPN. In this research, smoking, being older than 40, and male gender were the main factors linked to DPN. Since 1990, Diabetes mellitus has become more common gradually in India, and this trend is expected to continue in the coming years. With 4% of all DALYs in India in 2016, diabetes was ranked as the country's fourth most common reason for life years adjusted for disability (DALYs) 2. In India,

Prevalence of Diabetic Neuropathy Worldwide

Devices and straightforward clinical bedside techniques may aid in the early detection of DN and avoid complications such as foot ulcers, eventually resulting in amputation(16). Diabetic neuropathy (DN) is seen in people with diabetes type 1 mellitus in 28.70% of cases worldwide, while type 2 diabetes mellitus patients have a frequency of 50.70% of cases1. In individuals with type 2 diabetes, the incidence of DN was reported to be 39.3% in six major Indian cities. The incidence of DN among persons with diabetes in the US is thought to be 28%. The total prevalence of DN among individuals with diabetes was reported to be 28% in a cross-sectional survey given to a sample of adults in the United States aged 40 and older. Age, the length of diabetes, the HbA1c score, and hypertension were independently linked to the prevalence of the DN.(16-17) The estimated prevalence of DN in the Americas and the Caribbean (LAC) was 46.5% (95%CI: 38.0--55.0), with a significant variation ($I2 = 98.2\%$; $p<0.01$). The primary causes of heterogeneity linked to increased prevalence were insufficient sample size, increased A1c (%), and diagnostic criteria.(17)

In conclusion, diabetic neuropathy is a frequent consequence among individuals with diabetes, while its incidence varies greatly across various communities worldwide. Frequent screening with low-cost

Table 1: Global Prevalence of Diabetic Neuropathy by Region

Region	Prevalence (%)	Confidence Interval (95%)	Key Notes
Worldwide (Type 1 DM)	28.70	N/A	Based on global estimates
Worldwide (Type 2 DM)	50.70	N/A	Higher in Type 2 patients
India (Major Cities)	39.3	N/A	Urban-focused studies
United States	28	N/A	Cross-sectional survey, adults 40+
Latin America & Caribbean	46.5	38.0-55.0	High heterogeneity (I2=98.2%)

IMPACT ON QUALITY OF LIFE

Patients with DM who have diabetic neuropathy have a significant decline in their QOL. The Nottingham Health Profile (NHP) domains showed significantly greater scores (impaired QOL) for patients alongside symptomatic diabetic neuropathy; this was the case when compared to the non-diabetic controls and the other 79 patients with type 2 as well as type 1 diabetes. I.e. Sleep, physical mobility, discomfort, energy, and emotional response were some of these areas. Additionally, compared to the non-diabetic group of controls, the diabetic patients lacking neuropathy had substantially worse QOL for 4/6 NHP domains, suggesting that DM itself may lower QOL.(19-20)

Both painful and non-painful forms of diabetic polyneuropathy (DPN) have a major negative impact on patients' quality of life (QOL) 3. Eighty individuals who had painful DPN and eighty with DPN but no neuropathic pain participated in the research, which found that painful DPN is a significant factor influencing many areas of quality of life in those with diabetes. For the SF-36 standardized questionnaire, which measures quality of life, patients with painful DPN had much worse values in all eight categories and both summary scores when compared to individuals without neuropathic pain.(21)

It was shown that type II diabetes patients' health-related quality of life was significantly impacted by diabetic peripheral neuropathic pain, with the "role physical" and "mental health" domains suffering the most. The existence of diabetes-related complications, advanced age, prolonged sickness, and enhanced pain perception of all have shown to have a detrimental impact on health-related quality of life.(22) Patients have a considerable reduction in QOL due to diabetic neuropathy, especially when it is severe. There are several dimensions to the effect, including social, physical, and emotional aspects of existence. Thus, to enhance the quality of life for diabetic patients, diabetic neuropathy must be well managed.

PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY

According to current views on the pathogenesis of DNP, a number of variables, including inflammation, oxidative stress, hyperglycaemia, and hereditary susceptibility, may contribute to the illness.

It is well acknowledged that hyperglycemia is a major factor in the onset of neuropathy caused by diabetes. Increased blood glucose levels may alter the chemical composition of nerves, reducing their capacity to carry impulses. This may cause damage to the nerves in your hands and feet, resulting in symptoms including tingling, numbness, and discomfort (23).

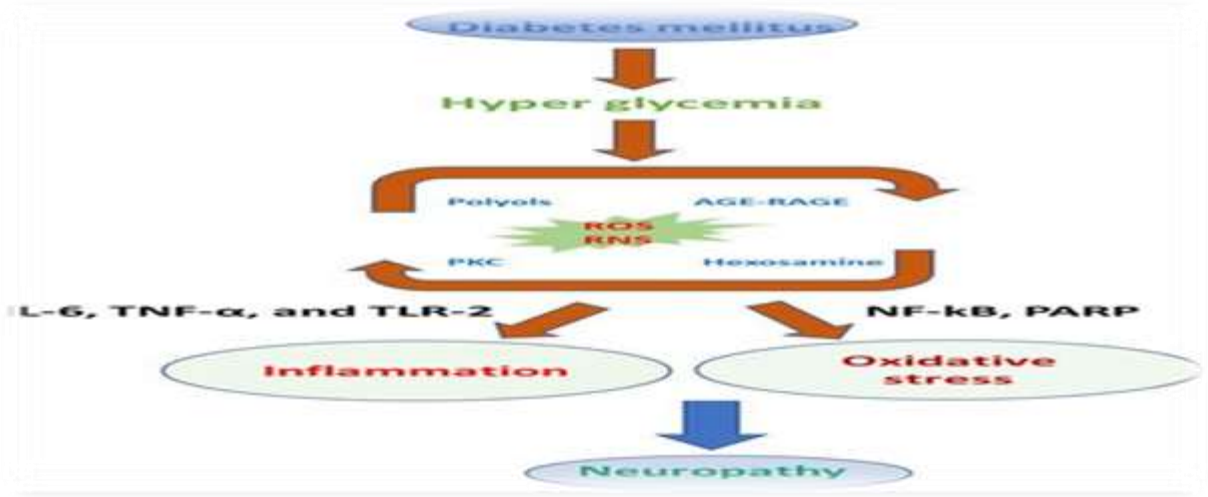

Figure 1: Photographical Representation of Oxidative Stress in Development of Neuropathy

INFLAMMATION

Long-term hyperglycemia initiates a downstream metabolic cascade that causes peripheral nerve injury through a variety of mechanisms, including enhanced polyol pathway flux, enhanced production of advanced glycation end products, excessive cytokine release, activation of protein kinase C, and oxidative stress. This is the inflammatory pathophysiology of diabetic neuropathy. Diabetic neuropathy develops and worsens as a result of this inflammatory reaction.(24)

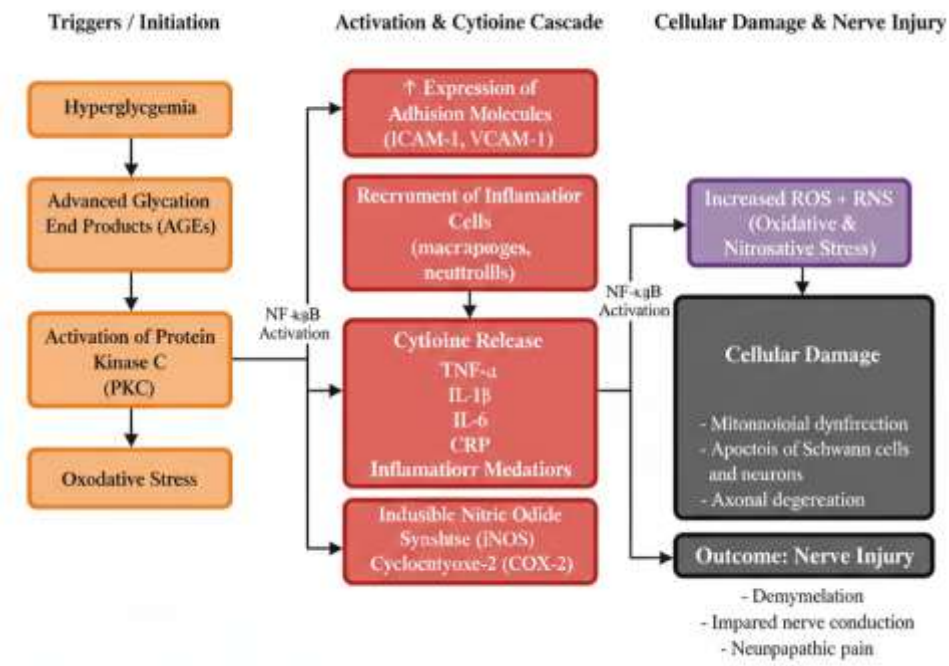

Figure 2: Inflammatory Pathway of Pathophysiology

Obesity, overt metabolic syndrome, insulin loss and resistance, hyperglycemia, and other variables interact intricately in the inflammatory pathogenesis of diabetic neuropathic pain. These elements cause inflammatory processes to be activated, which exacerbates diabetic peripheral neuropathy's (DPN) nerve

damage and discomfort (25). Two of the main causes of DPN are insulin resistance or loss and hyperglycaemia. A sudden drop in HbA1c brought on by insulin treatment in a rodent model of diabetes type 1 resulted in the occurrence of a mild neuropathy alongside inflammatory components, indicating that information from human tissues along with intervention trials may support the inflammation-related pathogenesis of DPN.(25)

Potential markers of DPN include inflammatory biomarkers such TNF-, cytokines that promote inflammation, interleukins-1b, 2, 6, and 8, and tumour necrosis factor-alpha. Studies examining these biomarkers' clinical value in identifying high-risk patients and directing therapies should be the main emphasis since it can be early indicators of DPN.(26)

CURRENT TREATMENT CHALLENGES

One major obstacle to the treatment of diabetic's neuropathic pain is insufficient pain alleviation. There are several drawbacks and difficulties with the existing treatments available for diabetic neuropathic pain (DNP), such as insufficient pain alleviation, adverse effects, and low patient adherence.

To begin with, one of the biggest challenges in treating DNP is insufficient pain treatment. Only 30% of patients get pain relief from the current pharmacologic ideas that are advised by worldwide recommendations, and until recently, there was no comprehensive, unambiguous categorization of NP, which led to underdiagnosis along with undertreatment.(31)

Antidepressant

Furthermore, one typical drawback of the DNP therapy choices available today is their potential for adverse effects. For example, the intrathecal form of administration of dextromethorphan, which has been demonstrated to be beneficial in relieving the painful symptoms underlying diabetic neuropathy, has a fundamental drawback that might result in side consequences. Comparably, adverse effects from antidepressants used to alleviate pain, such as weight gain, sleepiness, dry mouth, and dry eyes, might affect patient adherence to treatment.(32)

Gabapentin

There are drawbacks to using these drugs. For example, frequent adverse effects of gabapentin, including diarrhoea and dry mouth, are seldom seen at the modest dosages used for neuropathic pain.(33)

SNR (Selective Noradrenaline Reuptake Inhibitor)

A typical medication for treating depression, duloxetine is a selective noradrenaline reuptake inhibitor that may also be used to treat DNP. Constipation, nausea, and somnolence are among the major adverse responses to duloxetine, which is normally well tolerated.(33) The last major issue in managing DNP is low patient adherence. Few drugs are successful, with just three FDA-approved treatments for PDN at this time2. Despite having access to several treatment choices and recommendations, none are adequate. Moreover, the intricacy of handling DNP might affect patient adherence and result in less-than-ideal results since it necessitates strict glucose control and the usage of several drugs.(31)

The drawbacks and difficulties with the DNP treatments available today include insufficient pain alleviation, adverse drug reactions, and low patient compliance. A multimodal strategy will be needed to address these issues, including the creation of novel treatment choices, more patient involvement and education, and better control of the DNP's underlying processes.

Table 2: Common Treatments for DNP and Their Challenges

Treatment Type	Examples	Key Challenges	Adverse Effects

Antidepressants	Duloxetine, Dextromethorphan	Low efficacy (30% relief), poor adherence	Weight gain, sleepiness, dry mouth
Gabapentin	Gabapentin	Modest doses limit side effects but insufficient relief	Diarrhoea, dry mouth
SNRIs	Duloxetine	Low patient compliance	Constipation, nausea, somnolence
Others	Various FDA-approved	Underdiagnosis, undertreatment	General side effects, complexity

Role of Antioxidants in the Treatment of Diabetic Neuropathic Pain

Antioxidants serve a critical role in lowering oxidative stress, and inflammatory processes and guarding against nerve damage in neuropathy caused by diabetes. In the setting of neuropathy caused by diabetes, oxidative stress is a substantial contributor to damage to the nerves, and antioxidants operate by neutralizing damaging free radicals and minimizing oxidative harm to nerve cells. Antioxidant substances may thus affect the endoneurial oxidative equilibrium via several methods. The information at hand indicates that the majority of antioxidants have a significant impact on nerve microcirculation. The only possible explanation for the restoration of the oxidative equilibrium in the nerve after antioxidant therapy is increased tissue oxygenation. According to recently released evidence assessing the impact to glucose on mortality in cultured neurons, OD not only causes vascular alterations but also directly contributes to nerve dysfunction. As a result, antioxidants' direct effects on neurons should not be disregarded.(30)

DN treatment always starts with maximizing glucose control, followed by pain management. Although encouraging preclinical findings with inhibitors of important pathways are not unexpected given the involvement of OD or related variables in the development of DN, the ultimate choice is based on outcomes of clinical studies. Antioxidants should be used in addition of standard therapy if oxidative stress is only thought to the a minor factor in DN. It is still difficult to develop novel medications to treat DN, and extensive long-term comparative studies are required.(34)

In diabetic neuropathy, antioxidants are necessary for lowering oxidative stress, decreasing inflammation, and preventing nerve damage. Antioxidants may be able to lessen the negative effects for oxidative stress on diabetic neuropathy nerve cells by scavenging free radicals, reestablishing the equilibrium between pro-oxidants along with antioxidants, and lowering inflammation. Antioxidants are very important for balance nerve function and slowing the course of diabetic neuropathy. Research on their therapeutic potential in managing and treating this devastating illness is still ongoing.(35)

Antioxidants in Diabetic Neuropathic Pain

A major consequence of diabetes which impacts the peripheral as well as autonomic nerve systems is diabetic neuropathy, which is mostly caused by oxidative stress. Diabetes causes hyperglycaemia, which increases the generation of free radicals that harm nerve cells' proteins, lipids, along with nucleic acids. Necrotic or apoptotic pathways may eventually cause nerve cell death as a consequence of this damage, which may also impair energy metabolism, signalling among cells, transport, and other critical activities.(43-44) In diabetics, hyperglycaemia causes oxidative stress via a number of different pathways. These include increased activity of the polyol pathway, nonenzymatic glycation via proteins, activation of PKC, and elevated flux of the hexosamine pathway. The excess synthesis of superoxide by the

mitochondria in response to hyperglycaemia causes disruptions in all of these processes, either directly or indirectly. Unchecked superoxide buildup and the ensuing increases in those pathways set off a cascade of progressively worsening cellular malfunction, which eventually results in diminished brain function and the loss in neurotrophic support of nerve cells.(43-45)

Oxidative stress (OS) has been proposed as a potential mechanism in diabetic neuropathy that may lead to endoneurial damage caused by oxidation and faulty nerve blood flow. Oxidative stress is exacerbated by excess glucose in neurons, which leads to the production of free radicals and ineffective antioxidant defences.(43) Reduced nerve blood flow, impaired neurotrophic support, and changes in endoneurial metabolism are some of the pathophysiological processes underlying diabetic neuropathy. Studies on animals have shown that antioxidants may prevent or repair the nerve dysfunction caused by hyperglycaemia. Oxidative stress (OS) may be the last common mechanism in the onset of diabetic neuropathy. The nutritive blood flow is corrected to mediate the effects of antioxidants, while direct impacts on the endoneurial oxidative status are not ruled out. Antioxidant medications, such as vitamin E and a-lipoic acid, have been shown in a small number of clinical trials to either lessen neuropathic pain or restore nerve conduction velocity.(46)

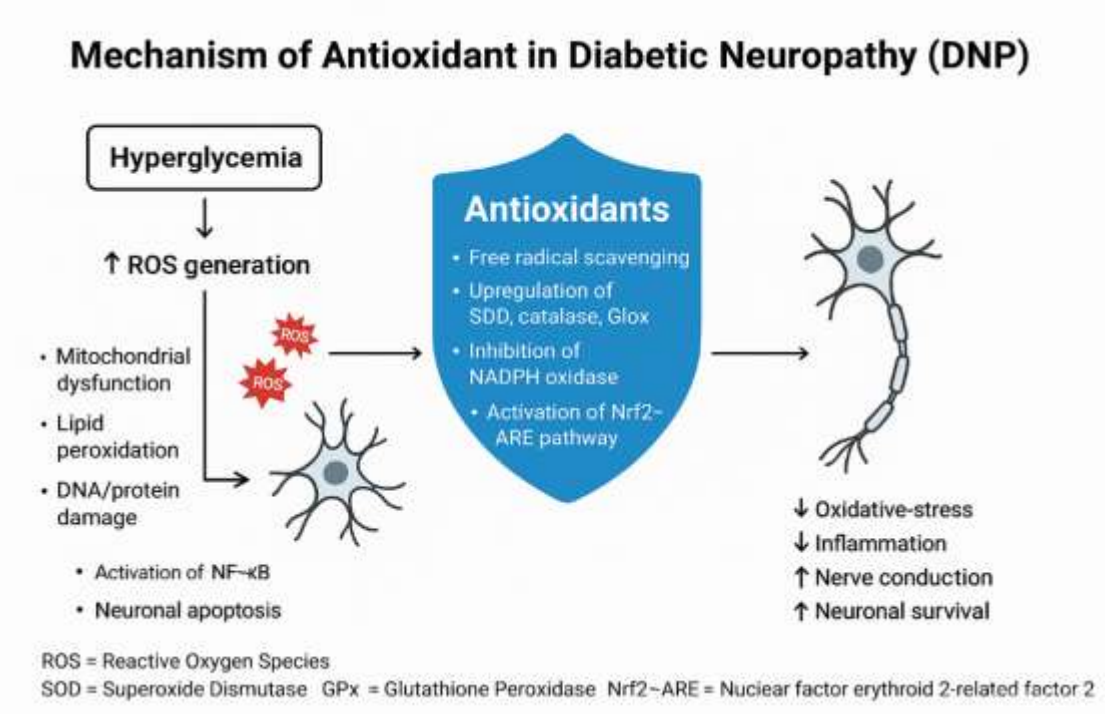

Figure 3: Mechanism of Antioxidant in DNP

In animal and cell-culture simulations of diabetes, as well as in clinical studies with antioxidants, the processes underpinning oxidative stress's role in chronic hyperglycaemia along with the onset of neuropathy have been investigated. There is compelling evidence linking diabetic neuropathy to oxidative damage caused by hyperglycaemia. As a result, developing more effective antioxidant treatments is still crucial to preventing neuropathy in diabetic patients.(47)

Evidence that antioxidants—more especially, vitamins C and E—have a significant impact on oxidative stress reduction in diabetic neuropathy via a number of mechanisms:(48)

- Preventing the production of harmful radicals known as free radicals
- Removing and neutralizing free radicals

- Elevating glutathione (GSH), a crucial antioxidant, in the cells(49)

According to studies, vitamin E and C plasma levels are lower in diabetic individuals with neuropathy, and oxidative stress indicators such superoxide anion, peroxynitrite 4, and 8-iso-prostaglandin F2α are higher. This shows that one of the main contributing factors to the Etiology of diabetic neuropathy is oxidative stress.(49-44)

Improved neuronal function has been linked to the administration of antioxidants such vitamin E to diabetic animal models. Furthermore, it has been shown that in individuals with diabetic peripheral neuropathy, antioxidant benfotiamine, an analogy of vitamin B1, decreases the production of advanced end products of glycation (AGEs) in tissue and oxidative stress.(48)

Other antioxidant treatments that have shown potential in the treatment of diabetic neuropathy consist of:(48)

- PKC inhibitors with antioxidant properties, such as ruboxistaurin.
- Aldose reductase inhibitors that decrease flow via the polyol pathway, such as ranirestat, epalrestat, and fidarestat, may lessen oxidative stress.
- PARP inhibitors, such as nicotinamide, have antioxidant properties and may lessen the effects of early-stage diabetic neuropathy. Demonstrate how antioxidants such as vitamin E and C may fight oxidative stress across a variety of ways, making them potentially effective treatment of diabetic neuropathy.

Mechanisms of Molecular Pathway

Through the following main pathways, vitamin C appears to contribute to the reduction of discomfort associated with diabetic neuropathy. Molecular Pathway for Targeting Vitamin C in Alleviating Diabetic Neuropathic Pain:

1. Strong anti-inflammatory and antioxidant qualities of vitamin C contribute to the protection of neurons and the mitigation of nerve damage brought on by diabetic neuropathy.(50)
2. Neurotransmitter synthesis modulation: Vitamin C promotes the synthesis of catecholamines with analgesic (pain-relieving) qualities, such as dopamine and norepinephrine.(50)
3. Prevention of excessive neuron stimulation and pain signalling: Vitamin C reduces the activity of glutamate-stimulated NMDA receptors and prevents glutamate from binding to NMDA receptors, which in turn prevents glutamate-induced neural excitation.(51)
4. Diminished oxidative stress and surface expression of NMDA receptors: Research has demonstrated that vitamin C supplementation can mitigate neuronal damage by lowering glutamate-induced over-activation of NMDA receptors and NMDA receptor surface expression. Neuropathic pain is lessened as a result.(52)

The proposed molecular pathway is illustrated below:

Molecular Pathway for Targeting Vitamin E in Alleviating Diabetic Neuropathic Pain(54)

1. **Antioxidant Properties of Vitamin E**:
    - By acting as an antioxidant, vitamin E lowers indicators of oxidative stress linked to diabetic neuropathy.
2. **Modulation of Oxidative Stress**:

- Neuropathic pain may be lessened by vitamin E because it lowers oxidative stress in the dorsal root ganglia.

3. **Scavenging of Lipid Peroxides**:
    - Lipid peroxides are scavenged by vitamin E, which lowers oxidative damage in diabetics.
4. **Regeneration of Reduced Glutathione**:
    - Reduced glutathione is necessary for cellular protective antioxidant systems, and vitamin E helps to regenerate it.

The potential of vitamin E to alleviate diabetic neuropathic pain is attributed to a combination of mechanisms, such as the regeneration of reduced glutathione, scavenging of lipid peroxides, modulation of oxidative stress within the dorsal root ganglia, and reduction in oxidative stress biomarkers.(54-55)

The flow chart figure shows how the antioxidant characteristics of vitamin E, together with its capacity to produce reduced glutathione, scavenge lipid peroxides, and regulate oxidative stress, can all work together to lessen the symptoms associated with diabetic neuropathic pain.

Molecular Routes for Aiming at Vitamins C and E Together to Reduce Diabetic Neuropathic Pain

1. **Synergistic Antioxidant Effects**(51)
    - When taken together, vitamins C and E have a synergistic antioxidant action that offers more protection against oxidative harm than when taken alone.
    - As lipid-soluble and water-soluble antioxidants, vitamin E and C can cooperate to target various facets of the oxidative damage pathway.
2. **Modulation of Oxidative Stress**(56):
    - Vitamin E works on the peroxidation of lipids process to shield polyunsaturated fatty acids against free radical assault, whereas vitamin C can lower the concentration of sorbitol, suppress aldose reductase, and lessen capillary fragility through oxidative stress
    - The synergy of these antioxidant pathways can help shield the neural system from oxidative stress brought on by diabetes.
3. **Regeneration of Antioxidant Defense**:
    - The antioxidant defense systems can be strengthened and molecular stability preserved by vitamin C's capacity to rebuild oxidized vitamin E.
    - The antioxidant system can be further strengthened by the combination of vitamins C and E, which can also improve glutathione peroxidase activity.
4. **Neurotrophic Support**(57):
    - The creation of neurotrophic factors, such as nerve growth factor (NGF), which are critical for maintaining the homeostasis and functionality of neurons, can be aided by vitamin C.
    - In addition to potentially alleviating neuropathic pain, the combination of vitamins C and E can help avoid the alterations that diabetes causes to the enteric nervous system.

The combined benefits of vitamin C and vitamin E are highlighted in the search results. These benefits include improved antioxidant protection, regulation of oxidative stress, rejuvenation of the antioxidant

system, and neurotrophic support. Although there isn't much direct clinical data about the use of vitamin C as well as vitamin E together to treat diabetic neuropathic pain, the underlying molecular pathways point to this combination as a potentially effective treatment strategy that merits more research.

The main chemical mechanisms by which vitamin C as well as vitamin E, alone or together, may be able to reduce diabetic neuropathic pain. The information that is now available emphasizes these vitamins' synergistic effects, antioxidant qualities, and ability to modulate oxidative stress. These characteristics may have a positive impact on the treatment of this crippling side effect of diabetes.

Previous Research on Vitamins C and Vitamin E in Diabetic Neuropathy

1. Using vitamins C and E to improve neuropathy scores in individuals with type 2 diabetes:(58)
    - Vitamin E supplementation has a neurotrophic effect in diabetic rats, and the deficiency of vitamins C and E in diabetes leads to the development of neuropathy.
2. Impact of vitamin E consumption on insulin resistance and glycemic management in individuals with diabetes:(59)
    - Consuming vitamin E lowers fasting insulin, HOMA-IR, and HbA1c levels in diabetic individuals, especially those having type 2 diabetes, considerably. The optimal daily amounts of vitamin E for regulating insulin and HbA1c are 400–700 mg.
3. How to Manage Diabetic Neuropathy with Antioxidant Strategies:(60)
    - Through a decrease in oxidative stress biomarkers, vitamin E has been shown to reduce the symptoms of diabetes and diabetes-related problems in animals; however, clinical studies did not demonstrate a statistically significant improvement in symptoms. The benefits of the A, C, and E vitamins in diabetes along with diabetic neuropathy require more investigation.
4. Combination vitamin C and vitamin E prevents enteric diabetic neuropathy:(61)
    - Vitamins C and E work together to have a synergistic impact that may help prevent diabetes-related alterations in the enteric nervous system and maybe reduce neuropathic pain.
5. Vitamin E and Evening Primrose Oil for the Treatment of Diabetes Mellitus-Associated Neuropathy:(62)
    - When combined with evening primrose oil, vitamin E is a safe and efficient way to manage mild to moderate neuropathy in people with diabetes mellitus. It also shows promising results in reducing the discomfort associated with painful neuropathy symptoms.
6. Treatment of Diabetic Neuropathy with Vitamin E and Alpha-Lipoic Acid:(63)
    - It was shown that individuals with diabetic neuropathy who took vitamin E along with alpha-lipoic acid together had improved nerve conduction velocity as well as reduced oxidative stress indicators, which may indicate a possible therapeutic benefit.
7. Vitamin C, E, and Alpha-Lipoic Acid in the Context of Diabetic Neuropathy:(53)
    - In human models of diabetic neuropathy, the combination of vitamin C, vitamin E, and alpha-lipoic acid showed synergistic benefits in lowering oxidative stress, enhancing nerve transmission, and easing neuropathic pain.

8. Mitochondrial Function and Vitamin E in Diabetic Neuropathy:(64)
    - It has been demonstrated that vitamin E preserves mitochondrial activity and lowers oxidative stress in diabetic rats' peripheral nerves, suggesting vitamin E's potential therapeutic use in diabetic neuropathy.
9. Vitamin E Supplementation's Impact on Oxidative Stress Indicators in Diabetic Neuropathy(55)
    - A recent investigation into the effects of supplementing with vitamin E on oxidative stress indicators in diabetic neuropathy was published in a prestigious scientific publication. The study demonstrated encouraging findings in lowering oxidative damage and enhancing nerve function.
10. Role of Vitamin C in Neurotrophic Support in Diabetic Neuropathy.(62)
    - In a recent study, the neurotrophic support that vitamin C offers in diabetic neuropathy was emphasized, along with its ability to boost neuronal function and nerve growth factor generation in diabetics.

REVIEW OF CLINICAL TRIAL AND OBSERVATIONAL TRIAL

Detailed Review of Studies on Vitamin C in Diabetic Neuropathic Pain

1. **Study 1**(51)
    - Source: Three hundred people with painful peripheral neuropathy who were type II diabetics participated in the study, which was carried out in Pakistan.
    - Intervention: 200 mg of oral vitamin C and 60 mg of duloxetine were given to the patients.
    - Results: At the 12-week mark, the intervention group outperformed the control group in terms of visual analog scores (VAS).
    - Conclusion: it was determined that vitamin C was a safe and affordable supplementary treatment for the discomfort brought on by diabetic peripheral neuropathy.
2. **Study 3**(66)
    - Source: Another study emphasized the role that antioxidant and anti-inflammatory qualities play in the analgesic mechanisms of vitamin C.
    - Key point: It has been discovered that vitamin C increases the production of dopamine and catecholamines, which helps reduce pain.
    - Conclusion: the study provided evidence in favor of vitamin C's potential to mitigate diabetic neuropathic pain, however further research is required to determine the long-term efficacy of this intervention in managing neuropathic pain.
3. **Study 4**(58)
    - Source: Diabetes Research along with Clinical Practice published a randomized controlled trial.
    - Intervention: Peripheral neuropathy and type 2 diabetes were present in 300 of the trial participants. Patients were given two doses of duloxetine per day: 60 mg of the drug alone and 200 mg of vitamin C.

- Results: Compared to the duloxetine-only group, the combination of duloxetine and vitamin C group saw noticeably higher improvements in neuropathy scores and quality of life after 12 weeks.
- Conclusion: the results indicate that vitamin C supplementation may be an advantageous supplementary treatment to enhance the prognosis of individuals suffering from diabetic peripheral neuropathy.

4. **Study 5**(64)
    - Source: A study published in the World Journal of Diabetes
    - Intervention: Using type 2 diabetic rats, the study examined the effects of a high-dose vitamin C supplement (1 g/kg/day) on cardiovascular autonomic neuropathy.
    - Results: Vitamin C treatment prevented the progression of myocardial autonomic neuropathy in diabetic rats by maintaining normal blood pressure, sympathetic tone, and heart rate variability.
    - Conclusion: the research indicates that elevated vitamin C levels may have the ability to safeguard the cardio-autonomic nerve and may be employed to stop the onset of cardiovascular autonomic neuropathy in individuals with type 2 diabetes.

Detailed Review of Studies on Vitamin E in Diabetic Neuropathic Pain

1. **Study 1**(67)
    - Source: The benefits of vitamin E high in tocotrienols on diabetic neuropathy were evaluated in a randomized, placebo-controlled study
    - Intervention: For eight weeks, participants were given tocotrienol-rich vitamin E orally.
    - Results: The study showed that vitamin E high in tocotrienols is effective in reducing the symptoms of diabetic neuropathy.
    - Conclusion: the research provided evidence in favor of tocotrienol-rich vitamin E being used as a diabetic neuropathy.

CONCLUSION

The study found that vitamin E and C in particular, an antioxidant supplement, helps patients with diabetic neuropathy feel less pain & have a higher quality of life. According to the findings, antioxidant tactics may be a useful complement to diabetic neuropathy treatment since they can lessen symptoms and enhance general health outcomes.

The study also discovered that in comparison to the control group, the combination of vitamins C and E with gabapentin, pregabalin, methylcoblamin, and nortriptyline significantly improved pain scores and quality of life. These results provide credence to the notion that antioxidant supplements may be a helpful supplemental treatment for diabetic neuropathy.

The study's findings align with earlier investigations were have demonstrated the advantages of antioxidants in lowering oxidative stress and enhancing nerve function in neuropathy caused by diabetes. The application of antioxidants, including vitamins C and E, has demonstrated the ability to decrease the production of AGEs and other oxidative damage indicators linked to diabetic neuropathy.

Antioxidant supplementation lowers pain scores: this study discovered that participants with diabetic neuropathy who took antioxidant supplements, especially vitamin E, had much lower pain levels. This is

in way with earlier studies that demonstrated the analgesic benefits of antioxidants in lowering pain under various circumstances.

Antioxidant supplementation enhances quality of life: This study discovered that participant with DN experienced a higher quality of life when taking antioxidant supplements, especially vitamin E. This is way with earlier research that demonstrated the positive impacts of antioxidants on life quality across a range of circumstances.

Combining antioxidants with treatments is effective: According to the study, taking vitamins C and E along with gabapentin, pregabalin, methylcoblamin, and nortriptyline significantly improved quality of life and pain scores when compared to those in the control group. This implied that antioxidant supplementation must be a helpful treatment adjunct for diabetic neuropathy.

Vitamins C and E have demonstrated potential in treating diabetic neuropathy, both separately and in combination. They function by enhancing neuronal function and lowering oxidative stress. They may be especially effective when combined to gabapentin, pregabalin, and their combination like nortriptyline medication that are currently prescribed to treat the illness. More research is necessary to completely comprehend the processes by which these antioxidants produce their positive benefits and ascertain the ideal supplementation amount and duration.

An important consideration in the treatment of diabetes neuropathic pain is medication adherence. Medication adherence has been reported to be positively impacted by vitamins C and E. Combination therapy utilizing both of these vitamins has been shown to improve adherence and lower pain levels.

Patients' quality of life is significantly impacted by medication adherence when they suffer from diabetic neuropathic pain. According to a study, patients who followed their prescription regimen scored higher on quality of life than those who did not.

Research have shown that combination therapy using vitamins C and E can improve medication adherence and lower pain levels to patients with diabetic neuropathic pain. According to a study, patients who received two of these vitamins C and E combined reported better rates of adherence and less pain than those who just received one of the vitamins.

Studies have shown that combination therapy using vitamins C and E can improve medication adherence and lower pain levels in patients who have diabetic neuropathic pain. According to a study, patients who took both vitamin C and E combined reported better rates of adherence and less pain than those who just received one of the vitamins.

Studies on DNP has shown that vitamins C and E improve treatment adherence. According to a study, patients who took vitamin E supplements reported greater rates of adherence as compared to those who with other medications.

This study indicates that participants with diabetes neuropathic pain frequently follow their prescription regimens poorly. Just 52.8% of individuals with diabetes peripheral neuropathic pain, for instance, followed their prescribed medication schedule, according to research.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future research on the following topics might be suggested in order to further advance our understanding of the role antioxidants in diabetic neuropathic pain population.

1. **Investigation and Gathering of Data**

- Long-term Outcomes Studies: Carry out long-term investigations to role of antioxidant affect life expectancy, quality of life, and the course of diabetic neuropathic pain.
- Data Analytics: Examine patient results and enhance antioxidants treatment regimens by using big data and artificial intelligence.

2. **Clinical Guidelines and Policies**
   - Establish and maintain defined clinical guidelines for the use of antioxidants in diabetic neuropathic pain to guarantee evidence-based and consistent procedures.
   - Insurance protection and Accessibility: Push for regulations that guarantee antioxidant treatment is included in insurance coverage, allowing all patients with diabetic neuropathic pain to have access to it.
3. **Improved ESA Compounds**
   - Extended-release tablets (ESAs): Created and used to enhance patient adherence and decrease dosage frequency.
   - Two other strategies to increase accessibility and save costs are to support the development and use of bio betters, which are enhanced copies of the original biologics, as well as biosimilars.
4. **Administration & Dosage**
   - Optimal dosage Strategies: To maintain goal glucose levels while reducing side effects, research the best dosage schedules and antioxidants formulations.
   - Route of Administration: Evaluate the advantages and disadvantages of intravenous vs subcutaneous delivery in various patient categories.

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