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The Protective Role of Vitamin D in Diabetic Peripheral Neuropathy- A Mini Review

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An increasing trend to sedentary life and poor dietary habits along with physical and mental stressors accelerate the incidence of type 2 diabetes (T2DM) Globally. The recent COVID-19 pandemic experience imposed an anxiety and fear specifically on the elders to become infected which again decreases mobility, and physical activities and fuels the incidence of T2DM. In addition to that, a homebound lifestyle creates vitamin D deficiency (VDD) that augments the severity and complications of having T2DM. The worsening condition of T2DM may give rise to diabetic peripheral neuropathy (DPN) that affects the body's peripheral nerves, has an impact on the sensations of the hands, arms, legs, and feet, and in more severe cases, the partial or total amputation of a toe, foot, or leg. DPN is a condition that's more prevalent in T2DM with an unknown cause and almost no effective treatments. The less controlled/uncontrolled hyperglycemia in T2DM generates harmful reactive oxygen species (ROS) that create oxidative stress (OS). The ROS-mediated redox regulation of the insulin signaling pathway makes the cell insulin resistant (IR) along with subsequent molecular changes leading to the pathogenesis of nerve cells. The cumulative effect of OS and VDD can make a person more vulnerable to DPN. Vitamin D (VD) is a potent antioxidant and can upregulate the expression of several antioxidant enzyme coding genes like catalase, and superoxide dismutase, can influence the activity of antioxidant enzymes such as glutathione peroxidase, glutamate cysteine ligase, glutathione reductase, and glucose-6-phosphate dehydrogenase etc. Antioxidant therapy with a modifiable factor like VD and alterations to one's lifestyle can potentially lower the OS and slow down the progression of T2DM and DPN.

Abbreviations

OS: Oxidative Stress
T2DM: Type 2 Diabetes Mellitus
DPN: Diabetic Peripheral Neuropathy
IR: Insulin Resistance
VD: Vitamin D
VDD: Vitamin D Deficiency
VDR: Vitamin D Receptor
ROS: Reactive Oxygen Species
NRF2: Nuclear Factor Erythroid 2-Related Factor 2
NGF: Nerve Growth Factor
EGFR: Epidermal Growth Factor Receptor
GDNF: Glial Cell Line-Derived Neurotrophic factor
PTH: Parathyroid Hormone
UVB: Ultraviolet B
AGEs: Advanced Glycation End Products
UDP-GlcNAc: Uridine-5-Diphosphate-N-Acetylglucosamine
PKC: Protein Kinase C
MAPK: Mitogen Activated Protein Kinase
TSS: Transcription Start Site
TAD: Topologically Associating Domain
VDREs: Vitamin D Response Elements
AREs: Antioxidant Response Elements
SNP: Single Nucleotide Polymorphism

Introduction

Diabetic peripheral neuropathy (DPN) is the most common complication and the primary cause of death and morbidity of individuals suffering from diabetes. DPN affects approximately 50% of people with diabetes [1]. Compared to type 1 diabetes, DPN is more prevalent in type 2 diabetes (T2DM) [2]. According to the estimates from the International Diabetes Federation, by 2030, worldwide the number of people with T2DM is predicted to reach 7079 per 100,000 and is expected to rise to 628 million by 2045 indicating a persistent increase across the globe [1,2]. The increasing burden due to factors like sedentary lifestyles, urbanization, lack of physical activity, chronic stress, mental health issues, and obesity may increase the risk of T2DM followed by DPN. DPN affects the body's peripheral nerves, which have an impact on the sensations of the hands, arms, legs, and feet and in severe cases, the partial or total amputation of a toe, foot, or leg [3]. Since currently there is no disease-modifying therapy for DPN, it is critical to identify it in its early phases and manage the conditions to lessen its burden.

Though the exact pathogenesis of DPN is not fully understood, oxidative stress (OS) in T2DM due to less controlled/uncontrolled blood sugar plays a key role in the onset and development of DPN [4,5]. Emerging findings indicate that Vitamin D deficiency (VDD) plays a crucial role in T2DM development [6-8] and might cause DPN in later life. T2DM usually develops over time. Some of the long-term causes of T2DM are excessive body weight, an unhealthy and poor diet, hypertension, chronic stress, a modern lifestyle of a more digitalised work nature than manual calorie expenditure, altered cholesterol and triglyceride levels, insulin resistance (IR), and (VDD) [6,9]. Among them, IR and VDD are the conditions that are present for a long span of life without any noticeable symptoms in individuals before the manifestation of T2DM and are often ignored. Thus, if a person has an inadequate level of VD as well as being in a state of IR and OS then the risk for T2DM increases. Therefore, managing and reversing the IR condition and maintaining optimum VD levels can help in preventing or delaying T2DM and DPN. Inflammation, the other key reason behind DPN, shares a cause-effect relationship with OS. OS, through direct or indirect nerve injury, inflammation, apoptosis, poor blood flow, and mitochondrial dysfunctions, aids in the onset and progression of DPN [5,10,11]. Antioxidants play a vital role in combating OS by neutralizing Reactive Oxygen Species(ROS) and protecting cells from its toxic effects. VD, sunshine and fat-soluble vitamin, apart from its primary functions in the regulation of calcium and phosphorus, bone health, and immune system support, serves as a potent antioxidant as well as anti-inflammatory molecule. VDD is reported to be linked with several OS-linked diseases [12]. Several studies are showing that VDD plays a crucial role in causing T2DM [6-8] and that might be due to lack of its protective role on OS and inflammation.

VD (calcitriol) mediates its action through the vitamin D receptor (VDR). VD-VDR complex is responsible for regulating the mRNA expression of several antioxidant enzymes and NADPH oxidase [13-15]. In addition to that, VD controls the expression of nuclear factor erythroid 2-related factor 2 (NRF2) [16], a molecule involved in the antioxidant system signaling pathway that influences the expression of antioxidant enzymes [17]. VDD is also responsible for obesity, a global pandemic that fuels T2DM [18]. VD can cross the blood-brain barrier and has neuroprotective properties [19]. Additionally, it has been demonstrated that VD modulates pain by regulating the pain related genes like nerve growth factor (NGF), epidermal growth factor receptor (EGFR), and glial cell line-derived neurotrophic factor (GDNF); through VDR [20]. VDD can make fat stores more easily, and low VD levels can lead to increased parathyroid hormone (PTH) secretion [18,21]. Overly elevated PTH levels can promote fat storage while preventing fat breakdown [21]. VDR is expressed in adipocytes and indicates that VD regulates the majority of adipose tissue functions, including adipogenesis, endocrine function, and metabolic activity. This may raise the risk of obesity and other metabolic disorders linked to VDD [22].

The major cause of VDD is inadequate sun exposure, as the skin synthesises VD when exposed to ultraviolet B (UVB) rays. Several environmental factors like latitude, season, and weather conditions influence the availability of UVB rays, which determine the cutaneous synthesis of VD. Other factors such as sunscreen cream usage, clothing, outdoor activity, age, and skin tone also affect VD synthesis. Additionally, a diet deficient in foods high in VD, obesity, inflammation, certain medical conditions like nephrotic syndrome, fat malabsorption syndromes, bariatric surgery, and patients taking several medications may interfere with VD absorption [23]. However, apart from these, certain genetic factors also interfere with the VD levels [24,25,26] as a significant percentage of the global population suffers from VDD even with ample exposure to sunlight and consumption of VD-rich foods, and these might be due to single nucleotide polymorphisms (SNPs) in the VDR and other VD metabolising genes.

Research has provided evidence to support the notion by

demonstrating the relationship between VDR polymorphisms and how they influence VD levels [27,28]. This review aims to emphasize the critical links between DPN and T2DM with OS and VDD highlighting the protective role of VD as a modifiable antioxidant as well as an anti-inflammatory agent.

Discussion

Diabetic Peripheral Neuropathy, T2 DM and Oxidative Stress

Hyperglycemia, or elevated blood sugar in T2DM, is one of the major causes behind the generation of ROS. Low to moderate amounts of ROS are beneficial for health, however, an imbalance between the production and inactivation of ROS and/or reduced activity of antioxidant systems generates OS [29]. OS is one of the key processes that, by involving several mechanisms and influencing several pathways, plays a crucial role in DPN pathogenesis, resulting in peripheral nerve injury that can result in nerve dysfunction and neuropathic issues. In T2DM, high glucose levels can initiate a cascade that leads to increased production of ROS in nerve cells due to metabolic disruptions. T2DM causes an increase in the flux of glucose across numerous metabolic pathways, including the hexosamine and polyol pathways and the formation of advanced glycation end products (AGEs), all of which lead to the generation of ROS and oxidative damage to nerve cells. A minute elevation of ROS, particularly hydrogen peroxide, plays a vital role in the insulin signaling pathway by oxidizing and inactivating the cysteine residue of several phosphatases of insulin-stimulated phosphorylation cascade and making the cell IR [30,31].

In hyperglycemia, excess glucose is processed through the polyol pathway, leading to the conversion of glucose to sorbitol and then to fructose. This process consumes NADPH and generates reactive ROS, like superoxide radicals. Nerve cells are especially susceptible to this pathway due to high levels of the enzyme aldose reductase (responsible for glucose-to-sorbitol conversion). Excessive sorbitol accumulation within nerve cells results in osmotic stress and damage. Moreover, sorbitol conversion to fructose promotes glycation, increases AGEs, and depletes NADPH, causing a redox imbalance. Glucose flux through the hexosamine pathway is also increased in hyperglycemic conditions. As a result, UDP-GlcNAc (uridine-5-diphosphate-N-acetylglucosamine) levels rise which is a substrate for glycosylation, a post-translational modification of proteins. Excessive protein modification by glucosamine due to prolonged hyperglycemia may lead to changes in gene expression, and protein modifications can impact functions of transcription factor. These transcription factors are important regulators of many biological processes, including those involved in nerve function that might cause diabetic complications such as DPN. AGEs can bind to the receptor called RAGE and trigger inflammation, activate NADPH oxidases, and enhance OS, resulting in impaired nerve function and neuronal damage. In nerve cells, the accumulation of ROS may impair mitochondrial function. As energy production and the cellular balance depend on mitochondria, excess ROS and OS may disturb mitochondrial homeostasis, disrupt its chain of electron transport, damage mitochondrial DNA, and reduce the synthesis of ATP. Since mitochondria are abundant in axons, which have direct access to the nerve blood supply, nerve cells are more vulnerable to ROS-mediated damage due to high blood sugar. Furthermore, neurons' inability to detoxify excess ROS and their inability to produce sufficient amounts of ATP in hyperglycemic conditions can reduce the viability and function of nerve cells.

OS and oxidative damage also interfere with important signaling pathways, such as the activation of protein kinase C (PKC) and mitogen-activated protein kinases (MAPKs). PKC-β and PKC-δ are the two isoforms of PKC that are activated by hyperglycemia, leading to inflammation. PKC-β and PKC-δ can also activate NADPH oxidase, a powerful oxidant that contributes to OS. On the other hand, inflammation, along with PKC activation can also trigger OS. These, in turn, damage nerve fibers, impair nerve conduction, and lead to sensory and motor neuron dysfunction. Hyperglycemia also activates the MAPK pathway, particularly the JNK and p38 MAPK pathways that cause OS. When these kinases are activated, more proteins may become phosphorylated, which can start signaling processes linked to apoptosis, cellular stress responses, and inflammation. These, combined with high blood sugar, damage nerve cells, contributing to DPN. Hyperglycemia also influences and interferes with the PI3K/AKT signaling pathway, which provides neuroprotection and, if functions abnormally, may lead to impaired insulin signaling, neuronal dysfunction, reduced blood flow, inflammation, mitochondrial dysfunction, and neuronal apoptosis [10,11,32].

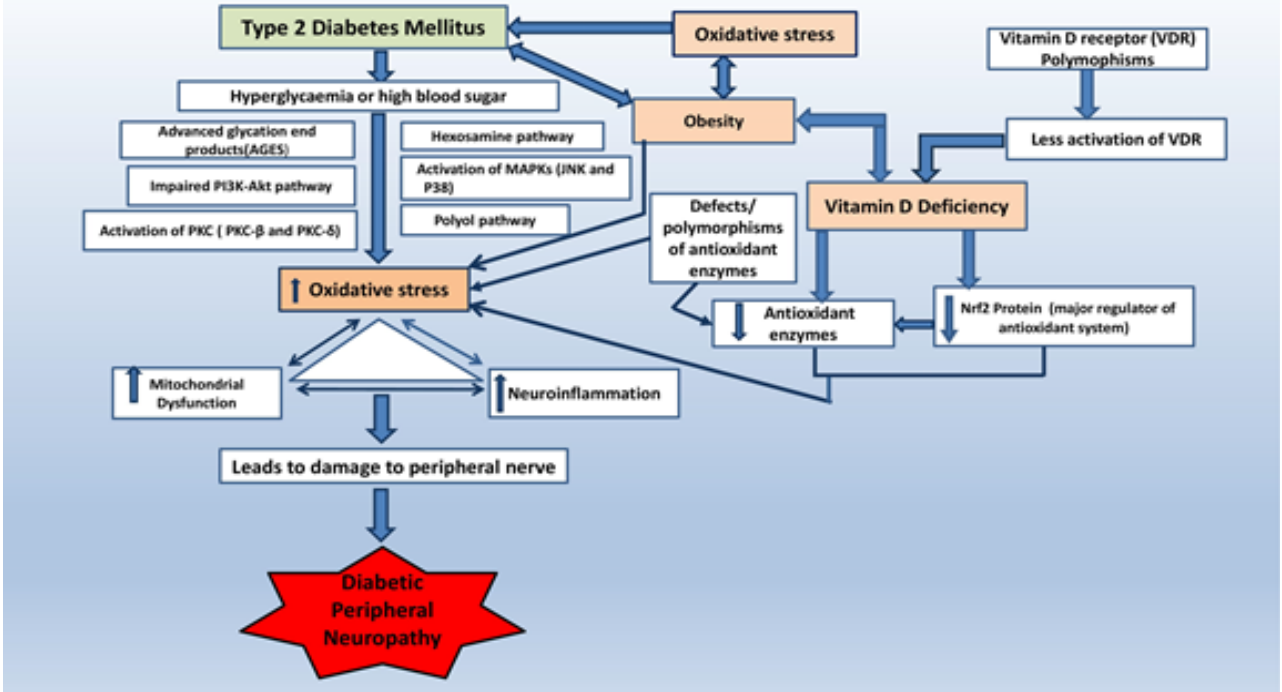
Role of Vitamin D in Antioxidant Defence Mechanism

Source and Mechanism of Action of Vitamin D

Antioxidants neutralize ROS and shield cells and tissues from oxidative damage. There are various antioxidant enzymes (superoxide dismutase, glutathione reductase/peroxidase, and catalase) apart from several vitamins (A, C, D, and E) and minerals (zinc, copper, selenium, and manganese) that serve as defence against OS [32]. Among the vitamins, VD is important

in the pathophysiology of several diseases associated with OS, where OS is primarily responsible for cellular damage through the accumulation of ROS, which limits the antioxidant defence system of the cell and ultimately results in cellular damage [12]. VD2 (ergocalciferol) and VD3 (cholecalciferol) are the two main forms of VD. The source of ergocalciferol is plants, while cholecalciferol is obtained from animal sources as well as produced in the skin when exposed to UVB radiation from the sun. VD (both VD2 and VD3) undergo two hydroxylation processes to become active. It first undergoes conversion in the liver by 25-hydroxylases (under the regulation of CYP2R1, CYP27A1, CYP3A4, and CYP2J2 gene) to 25-hydroxyvitamin D [25(OH)D]. Subsequently, 1α-hydroxylase (under the regulation of the CYP27B1 gene) in the kidneys transforms it into its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D]. Vitamin D-binding protein (GC) facilitates the specific transportation of VD in the bloodstream and its metabolites to target tissues or storage sites [22,33]. The deficiency of VD is found to be associated with several factors that contribute to various health conditions, affecting people of all ages and ethnicities around the world. It is well known that the active form of VD (calcitriol) binds to its nuclear receptor VDR inside cells to control target gene expression either by enhancing or suppressing it [12]. As a transcription factor, VDR binds to the enhancer region, which has a site to bind with other transcription factors, and these enhancer regions can be located both upstream and downstream of the transcription start site (TSS) of a gene [33].

Figure 1: Hyperglycemia, Oxidative stress and Vitamin D deficiency in the development of Diabetic Peripheral Neuropathy



Vitamin D as an Antioxidant

VD-activated VDR binds to specific DNA sequences called vitamin D response elements (VDREs) in the promoter region of their target genes, influencing their rate of transcription [33]. One such category of target genes is the antioxidant enzyme genes, as the reports show that VD or its supplementation influences the mRNA expression and increases the activity of antioxidant enzymes such as catalase (convert hydrogen peroxides into water and molecular oxygen) [34],superoxide dismutase (convert superoxide radicals into hydrogen peroxide and molecular oxygen) [12,35], and g-glutamyl transpeptidase, which aids in the synthesis of glutathione. VD also influences the activity of other antioxidant enzymes such as glutathione peroxidase (convert hydrogen peroxide into water and oxygen), VD also increases the activity of glutamate cysteine ligase, glutathione reductase, and glucose-6-phosphate dehydrogenase, which aid in the formation of glutathione, that upregulate glutathione peroxidase. It has been evidenced that VD also down-regulates NOX enzymes, which produce harmful ROS [12,36,37].

Vitamin D and Nuclear Factor Erythroid 2-Related Factor 2 (NRF2)

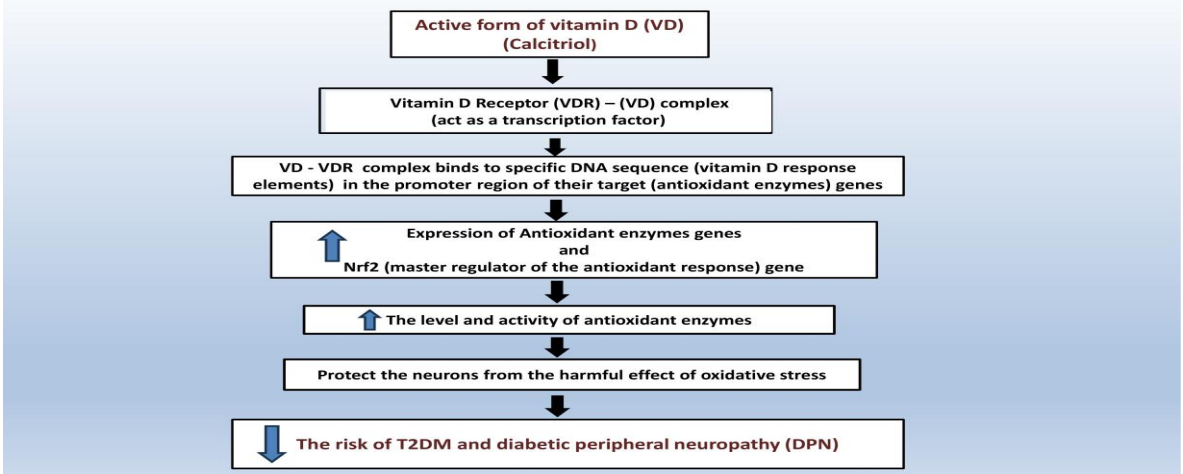
Numerous studies have demonstrated that VD significantly reduces OS biomarkers, demonstrating its beneficial impact in combating OS and its negative consequences [12]. Additionally, VD controls the NRF2 signaling pathway (a part of the wider

antioxidant response system), which is critical for promoting cellular defence mechanisms and protecting cells from OS. Research has indicated that the VD-VDR complex can upregulate the expression of NRF2 [16]. In the presence of an OS, NRF2 becomes activated, moves into the nucleus, and attaches itself to particular DNA sequences called antioxidant response elements (AREs) that are found in the promoter region of different antioxidant enzymes including catalase, superoxide dismutase-1, superoxide dismutase-2, glutamate-cysteine-ligase which is responsible for synthesizing glutathione, peroxyredoxins, thioredoxin, glutathione S-transferase, haemoxygenase-1 and NADPH-quinone-oxidase1 respectively [17,37]. NRF2 controls the expression of numerous genes involved in detoxification which are essential for the metabolism and removal of a wide range of hazardous chemicals, including xenobiotics and environmental toxins. NRF2 has been involved in the regulation of several cytochrome P450 family enzyme genes that play an important role in the metabolism of a variety of medicines and xenobiotics. NAD(P)H quinone oxidoreductase gene is also regulated by NRF2 which detoxifies quinones and protects cells from oxidative damage [37,38].

Vitamin D Deficiency and Polymorphism of Vitamin D Receptor

SNPs in the VDR gene were found to play a crucial role in VD level [27,28]. Some association studies reported that VDR-SNP is directly correlated with the severity of T2DM and a positive association exists between VDR gene variants and diabetes complications [39-41]. A group of researchers in Iran have shown a significant correlation between FokI polymorphism and diabetic foot ulcers while a study in Indonesia found that most of the individuals with diabetic foot with T2DM in a sunlight-rich area tended to have mutant VDR FokI polymorphisms and VDD [42,43]. Research in the Chinese population revealed a significant association between FokI-VDR polymorphism and diabetic retinopathy in T2DM individuals [44]. Hong YJ, et al. in their study on the Korean population showed BsmI polymorphism in the VDR gene with a lower risk of diabetic retinopathy in T2DM patients [45]. Research from the Czech Republic also showed a significant association between diabetic nephropathy and the FokI-VDR variant [46]. A meta-analysis study by Liu Z, et al. found that in Caucasians, the FokI variant in the VDR gene may have an impact on a person's vulnerability to diabetic neuropathy [47]. However, a study in Iran showed no significant difference between VDR gene polymorphisms of TaqI, ApaI, and rs4516035 in T2DM individuals with diabetic nephropathy, without nephropathy and healthy controls but their haplotype analysis showed that two haplotypes were significantly more frequent in diabetic nephropathy [48] Same observation was found in Polish population where VDR variants (Apa1, BsmI, FokI and TaqI) and risk to diabetic retinopathy in T2DM patients did not have any association [49]. In India VDR (rs1544410) association with decreased serum VD levels was studied in both micro-macrovascular complications of T2DM [50]. Furthermore, VDD association with DPN in T2DM individuals was also studied in Chinese and Turkish populations [51,52]. However, till now as far as our knowledge goes, there is no report on the study of the association of VDR polymorphisms concerning DPN in the Indian population. India is a huge, heterogeneous nation with a complicated history of human migration, cultural exchanges, and invasion with a diverse geography and complex demographic factors. Indian population possesses a mosaic pattern of genetic haplotypes and therefore, genetic polymorphism study in the Indian cohort might be varied from other ethnic populations of the world and deserves the attention of study in this area.

Figure 2: Vitamin D as an antioxidant in combating oxidative stress



Conclusion

Modern lifestyles, changing dietary habits, excessive screen timing, emotional and mental stress, and urbanization have raised the risk of OS and OS-related disorders. Moreover, the post-COVID era has been marked by an increased risk of OS, fat accumulation, and VDD, which in turn might raise the possibility of developing diseases linked to OS such as T2DM and later DPN. Thus, it can be hypothesised that when OS and VDD coexist in T2DM patients, they can have a cumulative effect on nerve damage, potentially increasing the risk of DPN. Therefore, maintaining an optimum level of VD might reduce the possibility of IR which can later cause T2DM, and if left unmanaged then DPN in the future. A deficiency or insufficiency of VD in T2DM individuals might also be a good candidate or predictor for DPN risk. Supplementation with VD and lifestyle modifications can help to manage DPN, which not only affects the quality of life of the affected individuals but also poses challenges for medical management and caregivers. Furthermore, as DPN is a complication of diabetes, any genetic predisposition that affects diabetes risk may influence the likelihood of developing DPN indirectly. Several studies have found a link between VDR and T2DM. Thus, an association study of VDR genetic polymorphisms and DPN may aid in the early detection, susceptibility, and prevention of DPN as well as personalized treatment strategies tailored to each patient's genetic profile. It will also aid in identifying the reasons why different treatment approaches may have varied effects on various ethnic populations. Accordingly identifying the modifiable and confounding factors that contribute to DPN and addressing them promptly is in dire need.

Conflict of Interest

The authors have stated that there is no conflict of interest.

Authors' Contributions

FB wrote the manuscript and prepared the figures.

BRB designed, reviewed, and approved the manuscript.

FB=Farzana Begum, BRB=Barnali Ray Basu

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References

1. Iqbal Z, Azmi S, Yadav R, Ferdousi M, Kumar M., et al. (2018) Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. Clin Ther 40: 828-849.
2. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, et al. (2020) Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health10: 107-111.
3. Hicks CW, Selvin E (2019) Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. Curr Diab Rep 19: 1-8.
4. Ko SH, Cha BY (2012) Diabetic peripheral neuropathy in type 2 diabetes mellitus in Korea. Diabetes Metab J 36: 6-12.
5. Lin Q, Li K, Chen Y, Xie J, Wu C, et al. (2023) Oxidative stress in diabetic peripheral neuropathy: Pathway and mechanism-based treatment. Mol. Neurobiol 28 :1-21.
6. Taderegew MM, Woldeamanuel GG, Wondie A, Getawey A, Abegaz AN, et al. (2023) Vitamin D deficiency and its associated factors among patients with type 2 diabetes mellitus: a systematic review and meta-analysis. BMJ open 13: e075607.
7. Vijay GS, Ghonge S, Vajjala SM, Palal D (2023) Prevalence of Vitamin D Deficiency in Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study. Cureus 15: e38952.
8. Alhumaidi M, Adnan AG, Dewish M (2013) Vitamin D deficiency in patients with type-2 diabetes mellitus in southern region of Saudi Arabia. Maedica 8: 231.
9. Wondmkun YT (2020) Obesity, insulin resistance, and type 2 diabetes: associations and therapeutic implications. Diabetes Metab Syndr Obes 9: 3611-3616.
10. 10. Hosseini A, Abdollahi M (2013) Diabetic neuropathy and oxidative stress: therapeutic perspectives. Oxid Med Cell Longev.
11. Ye D, Fairchild TJ, Vo L, Drummond PD (2022) Painful diabetic peripheral neuropathy: Role of oxidative stress and central sensitisation. Diabet Med 39: e14729.
12. Sepidarkish M, Farsi F, Akbari Fakhrabadi M, Namazi N, Almasi Hashiani A, et al. (2019) The effect of vitamin D supplementation on oxidative stress parameters: a systematic review and meta-analysis of clinical trials. Pharmacol Res 139:141-152.
13. Mastali VP, Hoseini R, Azizi M (2023) The effect of short-term vitamin D on the antioxidant capacity following exhaustive aerobic exercise. Afr Health Sci 23: 584-591.
14. Masjedi F, Keshtgar S, Zal F, Talaei-Khozani T, Sameti S, et al. (2020) Effects of vitamin D on steroidogenesis, reactive oxygen species production, and enzymatic antioxidant defense in human granulosa cells of normal and polycystic ovaries. J Steroid Biochem Mol Biol 197:105521.
15. Velimirović M, Jevtić Dožudić G, Selaković V, Stojković T,

Puškaš N, et al. (2018) Effects of vitamin D3 on the NADPH oxidase and matrix metalloproteinase 9 in an animal model of global cerebral ischemia. Oxid Med Cell Longev 2018: 3273654.

16. Nakai K, Fujii H, Kono K, Goto S, Kitazawa R, et al. (2014) Vitamin D activates the Nrf2-Keap1 antioxidant pathway and ameliorates nephropathy in diabetic rats. Am J Hypertens 27: 586-595.
17. Hayes JD, Dinkova-Kostova AT (2014) The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci 39: 199-218.
18. Vanlint S (2013) Vitamin D and obesity. Nutrients 5: 949-956.
19. Holick MF (2015) Vitamin D and brain health: the need for vitamin D supplementation and sensible sun exposure. Intern Med J 277: 90-93.
20. Habib AM, Nagi K, Thillaiappan NB, Sukumaran V, Akhtar S (2020) Vitamin D and its potential interplay with pain signaling pathways. Front Immunol 11: 820.
21. Marwaha RK, Garg MK, Mahalle N, Bhadra K, Tandon N (2017) Role of parathyroid hormone in determination of fat mass in patients with Vitamin D deficiency. Indian J Endocrinol Metab 21: 848-853.
22. Nimitphong H, Park E, Lee MJ (2020) Vitamin D regulation of adipogenesis and adipose tissue functions. Nutr Res Pract 14: 553-567.
23. Cashman KD (2020) Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing Calcified tissue international 106: 14-29.
24. Sepulveda Villegas M, Elizondo Montemayor L, Trevino V (2020) Identification and analysis of 35 genes associated with vitamin D deficiency: A systematic review to identify genetic variants. J Steroid Biochem Mol Biol 196: 105516.
25. Pal R, Choudhury S, Kumar H, Dey S, Das N, et al. (2023) Vitamin D deficiency and genetic polymorphisms of vitamin D-associated genes in Parkinson's disease. Euro J Neuroscience 58: 3362-3377.
26. Wang TJ, Zhang F, Richards JB, Kestenbaum B, Van Meurs JB, et al. (2010) Berry D, Kiel DP, Streeten EA, Ohlsson C, Koller DL, Peltonen L. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. The Lancet 376: 180-188.
27. 27. Gariballa S, Al-Bluwi GS, Yasin J (2023) Frequency of Vitamin D Receptor Gene Polymorphisms in a Population with a very High Prevalence of Vitamin D Deficiency, Obesity, Diabetes and Hypertension. Biomedicines 11: 1202.
28. Divanoglou N, Komninou D, Stea EA, Argiriou A, Papatzikas G, et al. (2021) Association of vitamin D receptor gene polymorphisms with serum vitamin D levels in a Greek rural population (Velestino Study). Lifestyle Genom 14 :81-90.
29. Karam BS, Chavez-Moreno A, Koh W, Akar JG, Akar FG (2017) Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes. Cardiovasc Diabetol 16: 1-9.
30. Lennicke C, Cochemé HM (2021) Redox regulation of the insulin signalling pathway. Redox Biol 42: 101964.
31. Chen XF, Wang L, Wu YZ, Song SY, Min HY, et al. (2018) Effect of puerarin in promoting fatty acid oxidation by increasing mitochondrial oxidative capacity and biogenesis in skeletal muscle in diabetic rats Nutr Diabetes 8: 1.
32. Pang L, Lian X, Liu H, Zhang Y, Li Q, et al. (2020) Understanding diabetic neuropathy: focus on oxidative stress Oxid Med Cell Longev 9524635.
33. Carlberg C (2022) Vitamin D and its target genes. Nutrients 14: 1354.
34. Middleton RP, Nelson R, Li Q, Blanton A, Labuda JA, et al. (2015) 1, 25-Dihydroxyvitamin D3 and its analogues increase catalase at the mRNA, protein and activity level in a canine transitional carcinoma cell line. Vet Comp Oncol 13:452-463.
35. Lisse TS (2020) Vitamin D regulation of a SOD1-to-SOD2 antioxidative switch to prevent bone cancer. Appl Sci 10: 2554.
36. Asghari S, Hamedi Shahraki S, Amirkhizi F (2021) Vitamin D status and systemic redox biomarkers in adults with obesity. Clin Nutr ESPEN 45: 292-298.
37. Berridge MJ (2015) Vitamin D cell signalling in health and disease. Biochem Biophys Res Commun 460: 53-71.
38. Ma Q (2012) Role of nrf2 in oxidative stress and toxicity. Annu Rev Pharmacol 53: 401-426.
39. Alfaqih MA, Araidah A, Amarin Z, Saadeh R, Al shboul O, et al. (2023) Association of vitamin D levels and polymorphisms in vitamin D receptor with type 2 diabetes mellitus. Biomed Rep 18: 1-10.
40. Abdeltif E, Charoute H, Barakat H, Rouba H (2014) Vitamin D receptor gene polymorphisms and vitamin D status and susceptibility to type 2 diabetes mellitus in Moroccans patients. Int. j. sci. res. publ 4: 1-8.
41. Al-Hazmi AS (2019) Association of vitamin D deficiency and vitamin D receptor gene polymorphisms with type 2 diabetes mellitus Saudi patients. Afr Health Sci 19: 2812-2818.

42. Soroush N, Radfar M, Hamidi AK, Abdollahi M, Qorbani M, et al. (2017) Vitamin D receptor gene FokI variant in diabetic foot ulcer and its relation with oxidative stress. Gene 599: 87-91.
43. Raflis R, Yuwono HS, Yanwirasti Y, Decroli E (2020) Vitamin D Receptor Gene Polymorphism FokI and 25-Hydroxy Vitamin D Levels among Indonesian Diabetic Foot Patients. Open Access Maced J Med Sci 8: 846-851.
44. Zhong X, Du Y, Lei Y, Liu N, Guo Y, et al. (2015) Effects of vitamin D receptor gene polymorphism and clinical characteristics on risk of diabetic retinopathy in Han Chinese type 2 diabetes patients. Gene 566: 212-216.
45. Hong YJ, Kang ES, Ji MJ, Choi HJ, Oh T, et al. (2015) Association between Bsm1 polymorphism in vitamin D receptor gene and diabetic retinopathy of type 2 diabetes in Korean population. Endocrinol Metab 30: 469-474.
46. Vedralová M, Kotrbova Kozak A, Železníková V, Zoubková H, Rychlík I, et al. (2013) Polymorphisms in the vitamin D receptor gene and parathyroid hormone gene in the development and progression of diabetes mellitus and its chronic complications, diabetic nephropathy and non-diabetic renal disease. Kidney Blood Press Res 36: 1-9.
47. Liu Z, Liu L, Chen X, He W, Yu X (2014) Associations study of vitamin D receptor gene polymorphisms with diabetic microvascular complications: a meta-analysis. Gene 546: 6-10.
48. Razi F, Meshkani MA, Zarrabi F, Sadr M, Asgarbeik S, et al. (2019) Haplotypes in vitamin D receptor gene encode risk in diabetic nephropathy. Gene 683: 149-152.
49. Cyganek K, Mirkiewicz Sieradzka B, Malecki MT, Wolkow P, Skupien J, et al. (2006) Bobrek J, Czogala M, Klupa T, Sieradzki J. Clinical risk factors and the role of VDR gene polymorphisms in diabetic retinopathy in Polish type 2 diabetes patients. Acta Diabetol 43: 114-119.
50. Ezhilarasi K, Dhamodharan U, Vijay V (2018) BSMI single nucleotide polymorphism in vitamin D receptor gene is associated with decreased circulatory levels of serum 25-hydroxyvitamin D among micro and macrovascular complications of type 2 diabetes mellitus. Int J Biol Macromol 116: 346-353.
51. He R, Hu Y, Zeng H, Zhao J, Zhao J, et al. (2017) Vitamin D deficiency increases the risk of peripheral neuropathy in Chinese patients with type 2 diabetes. Diabetes/Metabolism Research and Reviews 33: e2820.
52. Celikbilek A, Gocmen AY, Tanik N, Borekci E, Adam M, et al. (2015) Decreased serum vitamin D levels are associated with diabetic peripheral neuropathy in a rural area of Turkey. Acta Neurol Belg 115: 47-52.