American Journal of Biology and Natural Sciences
https://biojournals.us/index.php/AJBNS
ISSN: 2997-7185

Hyperglycemia Effects on Limbs Tingling and Twining Sensations

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Received: 2024, 15, Mar
Accepted: 2025, 21, Apr
Published: 2025, 31, May

Annotation: What Hyperglycemia Does to the Legs is quite devastated end with tragedy event of losing lower limbs, A patient with diabetic neuropathy (DN) may have both good and bad symptoms. On one hand, there are symptoms like pain, sensitivity, tingling, cramping, and cold feet. On the other hand, there are negative symptoms including sensory loss and delayed wound healing. The development and progression of DN cannot be explained solely by elevated blood glucose levels. New evidence suggests that a naturally occurring reactive metabolite called MG (methylglyoxal) can enhance function by modifying neuronal ion channels involved in chemo sensing and action potential generation in nociceptive nerve endings. This modification occurs after Glo1 "(glyoxalase I) levels are reduced. One possible reason for the development of DN is the effect of di carbonyls on the neuronal compartment.

Thus, there may be new and improved ways to treat DN if we focus on preventing the buildup and effects of MG."

Keywords: Numbness, Limbs Cramping, Higher Blood Sugar, nerve

damage, Peripheral neuropathy.

Introduction

Diabetes can cause a type of nerve damage known as diabetic neuropathy, which can manifest in any person who has diabetes. The presence of high blood sugar (glucose) was found to promote nerve damage throughout the entire body [1]. The most common nerves that were impacted were those that were located in the legs and feet. One way to determine the amount to which a diabetic patient's body is affected is to determine the degree of nervosa damage[2]."The symptoms of DN include discomfort and numbness in the legs and feet, as well as problems with the internal gastrointestinal tract, blood vessels, urinary tract, and heart. [3,4] Distal symmetric neuropathy is the most prevalent form of distal neuropathy, accounting for approximately 75% of all occurrences of the condition. Set-up neuropathy is a condition that can occur in diabetic people who have an asymmetric etiology. that, in the past, were brought on by metabolic changes and ischemia, but are today brought on by immunological alterations [3]". The objective sensory testing, nerve conduction analysis, and autonomic testing are the two of these five procedures that are recommended for use in the clinical laboratory examination of symptoms and signs associated with developmental neuropathy (DN)". Lipoic acid and L-carnitine, both of which are non-steroidal medications, should be provided to patients who are experiencing unpleasant neuropathic pain, analgesics, anti-inflammatory, antidepressant, and anticonvulsant symptoms in order to regulate hyperglycemia, which is a risk factor for cardiovascular disease. On the other hand, all diabetic people experience consequences such as neuropathy, in spite of the fact that this condition can be avoided or slowed down if blood sugar levels are regulated and a healthy diet is followed, the prevalence of this ailment continues to rise. It is Leukocytes, which are white blood cells, as well as other cells in the body, such as helper T cells of the second type Th2, are responsible for the secretion of interleukin-10, "which is a type of cytokine". It is shown to exhibit qualities that have the ability to regulate and change the immune response [5]. IL-10 also has the ability to reduce inflammation by limiting the generation of cytokines by immune cells. This is another way that it can reduce inflammation. Additionally, interleukin 10 plays a part in the enhancement of the production of antibodies by plasma cells, which in turn enables these cells to survive for a longer amount of time [6]. "Glial inflammatory responses are under control thanks to the presence of IL-10, which is expressed inside the central nervous system. It is common knowledge that interleukin-10 (IL-10) plays a vital role in the reduction of inflammation in the margins of the body. In addition, this particular molecule has been the anti-inflammatory cytokine that has been the subject of the most exhaustive research. Therefore, the biomarker IL-10 is commonly believed to be the epitome of an immunosuppressive cytokine that is produced within the central nervous system [7]. This is because IL-10 shows immune system suppression.

Glucose For Energy or Basic Materials

The body uses glucose, a basic carbohydrate, to provide energy quickly. Particularly for erythrocytes and the brain, a steady supply of glucose is necessary for energy. Glycolysis uses up the majority of glucose in a typical physiological setting, while the pentose phosphate pathway makes use of the rest [8]. Roughly 30% of glucose undergoes oxidation in the liver through the pentose phosphate pathway. Cells that divide quickly use the" NADPH-and ribose-dependent pentose phosphate pathway". In addition to being an essential component in many metabolic pathways, glucose is a cellular energy source. The body quickly turns glucose into glycogen, which is then stored in the muscles and liver, and this process eliminates the elevated blood glucose levels that occur after eating. The process of glycerol synthesis in adipose cells requires glucose. Glucuronic acid, an intermediate product of glucose oxidation, is involved in detox cation and the uranic acid pathways produce muco-polysaccharides. Sorbitol, which is naturally found in the eye's lens, can also be formed by reducing it. In addition to being an energy source, glucose is

a building block for neurotransmitters [9]. Since the brain is unable to retain glucose, it requires a steady flow of the fuel to keep working properly [10].

Glycemia to Excess

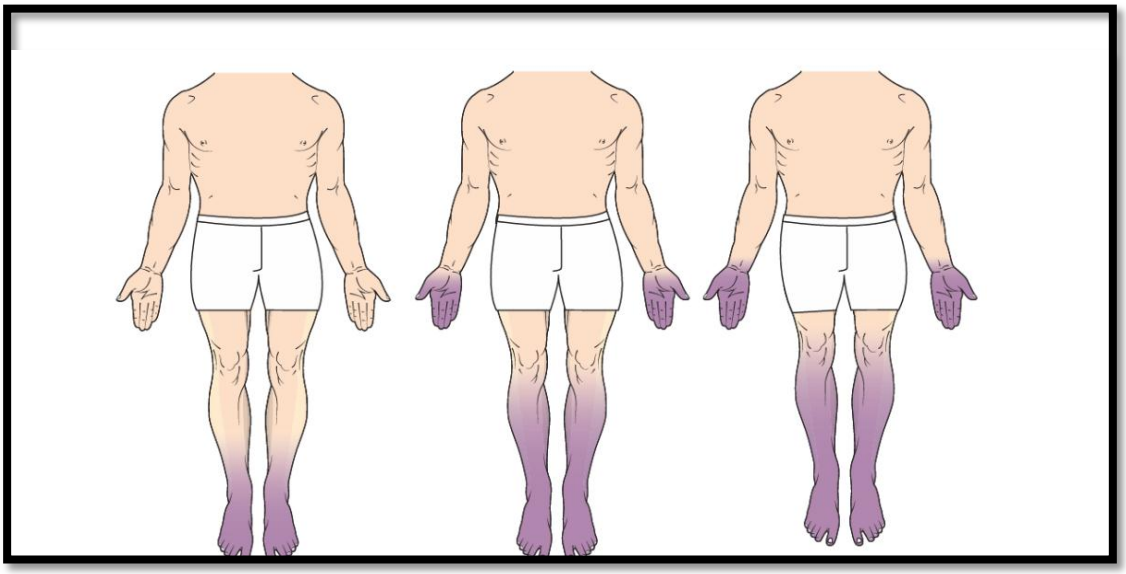
Hyperglycemia is characterized by persistently elevated blood sugar levels. Fasting hyperglycemia and postprandial hyperglycemia are suspected when blood glucose levels surpass 90-130 mg/dL following an 8-hour fast (10). When blood glucose levels rise above 180 mg/dL after eating, a condition known as postprandial hyperglycemia develops. The blood glucose level is considered to be hyperglycemic if it is between 100 and 126 milligrams per deciliter (about 5.6 and approximately 7 mill moles per liter), as stated by the standards of the American Diabetes Association. When the glucose level in the blood is higher than 7 mmol/L, the individual is deemed to have diabetes condition. Hyperglycemia that is chronic is one of the primary factors that contribute to organ damage. Hyperglycemia that is maintained for an extended period of time can have a number of detrimental consequences on many cell types, which can lead to glucose toxicity [11]. As a result of a multitude of investigations [11,12,13], the molecular pathways that under hyperglycemia and its repercussions have been identified. Since hyperglycemia causes reactive oxygen species (ROS) to be produced and It is possible that DNA is damaged [14,15], and it may also play a role in the development of an inflammatory response [16].

Research has demonstrated that hyperglycemia can promote both the polyol pathway and the hexamine pathway. Advanced glycation, the creation of end products (AGEs), and the activation of "protein kinase C (PKC) "are some of the additional variables that may contribute to the development of hyperglycemia [17]. Under conditions in which primary rat adipocytes were exposed to glucose, a decrease in insulin sensitivity was found [18]. Additionally, it has been proven that insulin resistance that is produced by hyperglycemia is not easily reversible [16]. The toxicity of hyperglycemia is exerted on a variety of macromolecules, including DNA and proteins, as well as organelles and cells. Hyperglycemia has also been linked to the development of microvascular and macrovascular problems in diabetic patients[19], which is a consensus that is widely well acknowledged. In the later stages of diabetes, problems such as nephropathy, retinopathy, neuropathy, atherosclerosis, and infection-prone conditions occasionally manifest themselves [13].There are a number of additional repercussions that may be connected with this illness [20]. Some of these consequences include hypothyroidism, hyperthyroidism, non-alcoholic fatty liver disease, decreased joint mobility, and fluid retention.

Polyneuropathy Caused By Diabetes

The most prevalent type of peripheral neuropathy is known as diabetic polyneuropathy with diabetes. The illness is present in around fifty percent of diabetic people who have either type 1 or type 2 diabetes, according to a comprehensive evaluation. There is a possibility that roughly fifteen percent of these patients will get symptomatic polyneuropathy [21]. Studies that only included hospitalized patients or studies that focused solely on clinical indications of polyneuropathy have produced prevalence numbers that are lower than those found in published research. The majority of the forms are sensory, with or without a minor degree of input from the motor system. Prickling, tingling, "pins and needles," burning, crawling, itching, electrifying, stinging, jabbing, and tight sensations in the legs, feet, hands, and fingers are some examples of positive sensory symptoms that are frequently experienced. Other examples include tingling, prickling, and "pins and needles." Several different sensations can be described using these sensations as a frame of reference. Warm stimuli have the potential to be misunderstood as being cold, and cold stimuli have the potential to be misunderstood as being either warm or hot. Both of these possibilities are possible. The emergence of discomfort from a range of causes is the defining characteristic of the disorder known as allodynia. typically harmless stimuli, is accompanied by nocturnal burning of the feet. There is a strong correlation between many of these symptoms and acute pain, which can sometimes become manage able. In most cases, the symptoms are symmetrical and initially limited to the toes. However, as time goes on, they expand

to more proximal portions of the feet, legs, and fingers (Fig.1). "As a result of the involvement of the sensory axon terminals factors that contribute to the development of foot ulcers. Early diabetic polyneuropathy is associated with a lower incidence of motor weakness; nonetheless, this weakness can later develop to distal weakness of foot and toe dorsiflexion, which puts patients at risk for falling". A waste of the intrinsic foot muscles is a symptom of weakness that is accompanied with weakness. Erectile dysfunction in men, distal loss of sweating, orthostatic symptoms such as "dizziness," and bowel and bladder dysfunction are all examples of symptoms that are commonly associated with concomitant disorders of the autonomic nervous system. It is vital to conduct a comprehensive neurologic examination in order to evaluate diabetic polyneuropathy since this examination offers a direct evaluation at a discounted cost. Even while it is reasonable to anticipate that there would be some variation in the findings, particularly in individuals who are experiencing the disease at an extremely early stage, the examination continues to be the gold standard for diagnosis. Quantitative methods or electro physiologic evaluation, which are considered auxiliary tests, do not replace the examination . .



(Fig.1): Illustration of progressive "stocking and glove" sensory changes in a patient with progressive diabetic polyneuropathy. "Sensory symptoms and signs begin in the distal territories of sensory nerves in the toes before fin gers with a gradual spread proximally". (From Zochodne DW, Kline G, Smith EE, et al: Diabetic Neurology. Informa Healthcare, New York, 2010, with permission.)"

In the distal region of the patient's body, there is a loss of sensitivity to light touch, pinprick, cold, and vibration with "a 128-Hz tuning fork", according to an examination of the patient's sensory capacities made by the medical professional. After obtaining anesthesia, patients who have a more severe sensory loss may not be able to discern between sharp (pinprick) and dull (analgesia) feelings, or they may not even be able to feel light touch at all. This is because they have lost the ability to perceive both types of sensations. As an additional component of the neurologic evaluation, the Semmes–Weinstein (10 g) monofilament test is a useful tool. Over the dorsum of the great toe or other specific areas of the foot, the filament is pressed against the skin until it forms a C-shaped bow for a single second. This is done during the procedure. After that, the patient is questioned about whether or not the stimulus is observed through the utilization of the probe. "Utilizing the Rydel–Seiffer tuning fork is a method that can be utilized to acquire semi quantitative information concerning the vibratory sensory perception". Depending on the degree of the ailment, the lack of vibration may impact the distal toes, the foot below the ankle, or even more extensive locations. "Furthermore, the condition may affect larger areas. With the exception of situations that are especially severe, testing for proprioceptive anomalies in the toes is typically considered to be considered normal". There is often a correlation between more severe sensory

loss and distal motor wasting, such as in the extensor digitorum brevis muscle, as well as accompanying weakness, notably in the region of foot and toe dorsiflexion. This is because distal motor wasting is associated with progressively more severe sensory loss. Both foot ulcers and a destructive arthro pathy caused by recurrent damage, which is referred to as a Charcot joint by medical professionals, are possible outcomes for patients. Foot ulcers are more common than a Charcot joint. A typical symptom of early diabetic poly neuropathy is the loss of the muscle stretch reflex at the ankle. This can occur in a number of different ways. All of the body's deep tendon reflexes are lost when the disorder is severe enough to cause irreversible damage. It is possible that the amount of sweating that has occurred has caused the feet to become dry. A loss of distal pulses and the appearance of femoral bruits are two symptoms that may be experienced by patients who are suffering from concurrent atherosclerosis. Persons who have involvement of the autonomic nervous system are more likely to suffer postural hypotension if they experience a drop in their systolic blood pressure of more than 20 mmHg or a drop in their diastolic blood pressure of 10 mmHg[22]. Consequently, it is necessary to conduct an assessment of the orthostatic vital signs.At [22,24]Subcategories of diabetic polyneuropathy have been formed on the basis of whether or not the ailment involves involvement of the patient's large or microscopic fibers .These subcategories have been established using the aforementioned criteria. persons who have large-fiber poly neuropathy are more likely to experience a loss of sensitivity to light touch, vibration, and proprioception than other persons. As an additional complication of this ailment, individuals may also face the possibility of experiencing ataxia of gait. Those who suffer from small-fiber polyneuropathy frequently experience autonomic dysfunction, and neuropathic pain, especially throughout the night, is also a prevalent symptom of this condition. As a result of this disease, pinprick and heat sensitivity are both impaired. A number of different kinds of diabetic polyneuropathy have been linked to the presence of pain that is characterized by neuropathic pain. The 23rd For the aim of conducting clinical research, a number of different methods have been applied over the course of time in order to assess the degree of severity of diabetic polyneuropathy. The San Antonio criteria classify polyneuropathy as class I if it does not exhibit any signs or symptoms but has abnormalities on electro physiologic testing, autonomic testing, or quantitative sensory testing (QST). This criterion was developed in the United States. Class II is characterized by either indications or symptoms, or both, depending on the degree to which the disease is considered severe [23] . There are twenty-four: Different scales for measuring neuropathy include the Modified Toronto Neuropathy Scale, the Utah Neuropathy Scale, the Michigan Neuropathy Scale, and the Mayo Clinic diabetic polyneuropathy classification., are some of the other scales that are not discussed in this page about neuropathy[25, 26 ,27].

Syndrome of the Carpal Tunnel

The transverse carpal ligament compresses the median nerve of the wrist, leading to carpal tunnel syndrome. Common causes of this ailment include using the thumb and wrist motions repeatedly. Tingling, soreness, and a lack of sensation in the thumb, index, and middle fingers are signs of this condition. Both waking up and going to sleep are associated with a worsening of these symptoms. Asymptomatic carpal tunnel syndrome can be diagnosed in 20 to 30 percent of diabetics with electrophysiologic testing[28,29]. Nevertheless, symptoms-presenting carpal tunnel syndrome is more common. Neuropathies affecting the upper limbs can be differentiated from carpal tunnel syndrome using electro physiologic testing that shows a selective slowing of median nerve fiber conduction across the carpal tunnel. Patients suffering from carpal tunnel syndrome may find relief by reducing their activity level and using wrist splints at night. There is only one operation available, and that is decompression, which involves severing the transverse carpal ligament ,may be thought of as a curative treatment[30]. "It is possible that non-diabetics' recoveries are more robust than diabetics', especially in cases when glycemic control is inadequate". Reason being, diabetic neuropathy makes nerve regeneration more difficult. Carpal tunnel syndrome, a type of entrapment neuropathy, is more common in both diabetic and non-diabetic patients. The incident is more likely to include the dominant hand than any other hand, and it disproportionately affects

women compared to males. "Tinel sign" refers to the process of tapping on the median nerve at the wrist in order to bring up positive sensory symptoms that are comparable to the patient's symptoms further away from the wrist. Even though the "Phalen sign—which involves flexing and holding both wrists against each other for one minute to simulate tingling—could be present, it is neither sensitive nor specific. For people with mild carpal tunnel syndrome, the symptoms might not be noticeable. Later on, the area around the median nerve could experience a loss of sensation. The abductor pollicis brevis, often called the thenar muscles, weaken and atrophy in more advanced forms of carpal tunnel disorder[30].

At the elbow, Ulnar Neuropathy Is Found.

When ulnar neuropathy is present at the elbow, the patient experiences pain and sensory problems in the middle half of the ring finger and the fifth digit. These symptoms can sometimes radiate into the palm and even reach the wrist near the elbow. These fingers, together with the medial volar and dorsal hand, all the way up to the wrist, are at risk of experiencing sensory loss. Because of the possibility of wasting and weakness of the intrinsic ulnar-innervated hand muscles, particularly in the first dorsal interposes muscle, the patient may have difficulty abducting or adducting their fingers while they are experiencing this condition. When the ulnar nerve in the elbow is manipulated, it is possible for the sensation to be sent to the hand, which in turn would duplicate the symptoms. Predisposing variables include the consumption of ethanol as well as previous elbow injuries or fractures. One of the most prevalent causes of the illness is when the patient leans on their medial elbow, which causes the nerve to become compressed. It is estimated that roughly two percent of persons who have diabetes mellitus have ulnar nerve entrapment when they are diagnosed with the condition.[29]. Reduced speed of ulnar motor and sensory transmission across the elbow, absence of action potentials from the ulnar sensory nerve and compound motor, and, in very unusual cases, a complete blockage of conduction across the elbow are all symptoms of this condition. Electro physiologic study has confirmed these results. Electromyography allows one to detect denervation when applied to the afflicted muscles. You can treat ulnar neuropathy by shifting your elbow or by cushioning the area around the nerve. These two approaches work well. If the lesion is affecting motor axons, is causing symptoms, and is getting worse despite conservative treatment, decompression may be the best option. Surgical decompression is a reasonable strategy in most circumstances, according to current clinical practice, even if there haven't been any controlled clinical trials done on diabetic patients to indicate that it improves long-term outcomes.

A Peripheral Neuropathy Caused by Diabetes

"It is typical for microvascular disorders of the eyes, kidneys, and peripheral nerves to develop resulting from both type 1 and type 2 diabetes' persistent hyperglycemia [31]. Usually beginning with the small nerve fibers of the lower limbs, diabetic peripheral neuropathy (DPN)"

Affects Nerve loss resulting from this disorder can induce a delayed start of symptoms including foot pain, tingling, numbness, muscular weakness, increased sensitivity to touch, and heat intolerance[32]. Patients describe a sensation like to that of a wooden or numb foot in either one or both feet, but first presentations of these symptoms may be modest and vague. Usually, the development of "DPN" is accompanied by a burning sensation marked by a "stocking and glove" distribution and that gets progressively more uncomfortable during the day [33]. The most often occurring sign of diabetic peripheral neuropathy" (DPN)" is distal symmetric limb numbness accompanied with loss of sensation. Furthermore, DPN can cause neuropathic pain in about twenty percent of diabetics as well. Pruritus, hyperalgesia, and induced pain rank as the most often occurring forms of pain [34]. Common forms of pain are, electrical, and cauterization extreme ones. Apart from this, the mix of hyperglycemia and metabolic disorders damages the immune system and influences its functioning in the body. Unnoticed and cunning, this cut could develop infected and seriously harm the limbs [35]. "The most common cause of non-traumatic lower limb amputation in most countries with high earnings, according recent studies, is distal proximal

neuropathy (DPN) "[36].

References

1. Feldman, E. L., Nave, K. A., Jensen, T. S., & Bennett, D. L. (2017). New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. *Neuron*, *93*(6), 1296-1313.
2. Yang, H., Sloan, G., Ye, Y., Wang, S., Duan, B., Tesfaye, S., & Gao, L. (2020). New perspective in diabetic neuropathy: from the periphery to the brain, a call for early detection, and precision medicine. *Frontiers in endocrinology*, *10*, 929.
3. Patil, S., Mhaiskar, A., Wake, P., & Mundhada, D. (2016). Diabetic Neuropathy: A Recent Trend. *World Journal of Pharmacy and Pharmaceutical Sciences*, *6*(1), 1610-20.
4. Patil, S., Mhaiskar, A., Wake, P., & Mundhada, D. (2016). Diabetic Neuropathy: A Recent Trend. *World Journal of Pharmacy and Pharmaceutical Sciences*, *6*(1), 1610-20.
5. Saraiva, M., Vieira, P., & O'garra, A. (2019). Biology and therapeutic potential of interleukin-10. *Journal of Experimental Medicine*, *217*(1), e20190418.
6. Schülke, S. (2018). Induction of interleukin-10 producing dendritic cells as a tool to suppress allergen-specific T helper 2 responses. *Frontiers in immunology*, *9*, 455.
7. Burmeister, A. R., & Marriott, I. (2018). The interleukin-10 family of cytokines and their role in the CNS. *Frontiers in cellular neuroscience*, *12*, 458.
8. Yan, L. J. (2014). Pathogenesis of chronic hyperglycemia: from reductive stress to oxidative stress. *Journal of diabetes research*, *2014*(1), 137919.
9. Dienel, G. A. (2012). Fueling and imaging brain activation. *ASN neuro*, *4*(5), AN20120021.
10. Mergenthaler, P., Lindauer, U., Dienel, G. A., & Meisel, A. (2013). Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends in neurosciences*, *36*(10), 587-597.
11. Szablewski, L. (2014). Diabetes mellitus: influences on cancer risk. *Diabetes/metabolism research and reviews*, *30*(7), 543-553.
12. Campos, C. (2012). Chronic hyperglycemia and glucose toxicity: pathology and clinical sequelae. *Postgraduate medicine*, *124*(6), 90-97.
13. Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. *Circulation research*, *107*(9), 1058-1070.
14. Asmat, U., Abad, K., & Ismail, K. (2016). Diabetes mellitus and oxidative stress—A concise review. *Saudi pharmaceutical journal*, *24*(5), 547-553.
15. Safi, S. Z., Qvist, R., Kumar, S., Batumalaie, K., & Ismail, I. S. B. (2014). Molecular mechanisms of diabetic retinopathy, general preventive strategies, and novel therapeutic targets. *BioMed research international*, *2014*(1), 801269.
16. Safi, S. Z., Qvist, R., Yan, G. O. S., & Ismail, I. S. B. (2014). Differential expression and role of hyperglycemia induced oxidative stress in epigenetic regulation of β1, β2 and β3-adrenergic receptors in retinal endothelial cells. *BMC medical genomics*, *7*, 1-13.
17. Sun, Q., Li, J., & Gao, F. (2014). New insights into insulin: The anti-inflammatory effect and its clinical relevance. *World journal of diabetes*, *5*(2), 89.
18. Rolo, A. P., & Palmeira, C. M. (2006). Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. *Toxicology and applied pharmacology*, *212*(2), 167-178.
19. Lu, B., Ennis, D., Lai, R., Bogdanovic, E., Nikolov, R., Salamon, L., ... & Fantus, I. G. (2001). Enhanced sensitivity of insulin-resistant adipocytes to vanadate is associated with

oxidative stress and decreased reduction of vanadate (+ 5) to vanadyl (+ 4). *Journal of Biological Chemistry*, *276*(38), 35589-35598.

20. Geraldes, P., & King, G. L. (2010). Activation of protein kinase C isoforms and its impact on diabetic complications. *Circulation research*, *106*(8), 1319-1331.
21. Baynes, H. W. (2015). Classification, pathophysiology, diagnosis and management of diabetes mellitus. *J diabetes metab*, *6*(5), 1-9 .
22. Dyck, P. J., Kratz, K. M., Karnes, J. L., Litchy, W. J., Klein, R., Pach, J. M., ... & Melton Iii, L. J. (1993). The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*, *43*(4), 817-817.
23. Ewing, D. J. (1988). Recent advances in the non-invasive investigation of diabetic autonomic neuropathy. *Bannister R.*
24. Malik, R. A., Veves, A., Walker, D., Siddique, I., Lye, R. H., Schady, W., & Boulton, A. J. M. (2001). Sural nerve fibre pathology in diabetic patients with mild neuropathy: relationship to pain, quantitative sensory testing and peripheral nerve electrophysiology. *Acta neuropathologica*, *101*, 367-374.
25. Anonymous. Report and recommendations of the San Antonio conference on diabetic neuropathy. Consensus statement. *Diabetes*. 1988;37:1000.
26. Bril, V., Tomioka, S., Buchanan, R. A., Perkins, B. A., & mTCNS Study Group. (2009). Reliability and validity of the modified Toronto Clinical Neuropathy Score in diabetic sensorimotor polyneuropathy. *Diabetic Medicine*, *26*(3), 240-246.
27. Singleton, J. R., Bixby, B., Russell, J. W., Feldman, E. L., Peltier, A., Goldstein, J., ... & Smith, A. G. (2008). The Utah Early Neuropathy Scale: a sensitive clinical scale for early sensory predominant neuropathy. *Journal of the Peripheral Nervous System*, *13*(3), 218-227.
28. Dyck, P. J., Kratz, K. M., Karnes, J. L., Litchy, W. J., Klein, R., Pach, J. M., ... & Melton Iii, L. J. (1993). The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*, *43*(4), 817-817.
29. AJ, W. (1999). Diabetic entrapment and compression neuropathies. *Diabetic neuropathy*, 481-508.
30. Kennedy, J. M., & Zochodne, D. W. (2000). The regenerative deficit of peripheral nerves in experimental diabetes: its extent, timing and possible mechanisms. *Brain*, *123*(10), 2118-2129.
31. Patoulias, D., Papadopoulos, C., Stavropoulos, K., Zografou, I., Doumas, M., & Karagiannis, A. (2020). Prognostic value of arterial stiffness measurements in cardiovascular disease, diabetes, and its complications: The potential role of sodium-glucose co-transporter-2 inhibitors. *The Journal of Clinical Hypertension*, *22*(4), 562-571.
32. Mukherjee, S., Ali, S., Hashmi, S., & Jahan, S. (2023). History, origin and types of neurological disorders. In *Applications of stem cells and derived exosomes in neurodegenerative disorders* (pp. 1-32). Singapore: Springer Nature Singapore.
33. Tavee, J., & Zhou, L. (2009). Small fiber neuropathy: a burning problem. *Cleve Clin J Med*, *76*(5), 297-305.
34. Sloan, G., Shillo, P., Selvarajah, D., Wu, J., Wilkinson, I. D., Tracey, I., ... & Tesfaye, S. (2018). A new look at painful diabetic neuropathy. *Diabetes research and clinical practice*, *144*, 177-191.

35. Jeffcoate, W. J., Vileikyte, L., Boyko, E. J., Armstrong, D. G., & Boulton, A. J. (2018). Current challenges and opportunities in the prevention and management of diabetic foot ulcers. *Diabetes care*, *41*(4), 645-652.

36. Boulton, A. J., Armstrong, D. G., Kirsner, R. S., Attinger, C. E., Lavery, L. A., Lipsky, B. A., ... & Steinberg, J. S. (2018). Diagnosis and management of diabetic foot complications.