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Glycosylated hemoglobin Hb1Ac, a biomarker of diabetic peripheral neuropathy DPN

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Abstract:

Background:

Diabetic peripheral neuropathy (DPN) is strongly correlated with morbidity and death. DPN raises the possibility of non-traumatic amputation by facilitating foot ulcers and gangrene. Evidence suggests that only modest glycemic management, as measured by hemoglobin (HbA1c) levels, can prevent neuropathy. Weakened time-subordinate glucose control may be associated with microvascular complications in diabetes. Glycemic variability is also known to be a possible marker of poor glycemic control and a sign of diabetic complications.

Objective: The objective of this study is to investigate the relationship between Diabetic peripheral neuropathy (DPN) and glycosylated hemoglobin level Hb1Ac (<7.0%).

Method: An observational clinical study where a total of 62 diabetes mellitus (DM) type 2 patients with diabetic peripheral neuropathy DM/+DPN group(32 females,39 Males, mean follow-up time 8 months, mean age 50±10 years, mean duration of diabetes diagnosis 12.1±9.5 years) and 10 type 1 diabetic patients without DPN (DM/-DPN group) were set as control. Blood samples were drawn from each patient and sent to the CPTH laboratory to analyze their glycemic profile.

Conclusion: In diabetics, there is a substantial correlation between elevated HbA1c levels and the development and progression of neuropathy. It is crucial to consider additional variables, such as the length of diabetes, coexisting medical conditions, and patient differences in response to therapy.

Keywords: Diabetic peripheral neuropathy, glycemic control HbA1c, Type 2 diabetes mellitus

Introduction:

Diabetes is a major global health concern. It results from either insufficient insulin production by beta cells (β cells) in the pancreas or inefficient insulin uptake by body cells, which leads to persistently elevated blood glucose levels. Approximately 425 million individuals worldwide were estimated to have diabetes in 2016 by the International Diabetes Federation. Both developed and developing nations are expected to see an increase in this number. By 2045, there will likely be 629 million diabetics worldwide if treatment and control of the condition are not addressed.[1] The following broad classifications apply to diabetes: Diabetes type 1 (caused by autoimmune destruction of β-cells, typically resulting in complete insulin insufficiency, including latent autoimmune diabetes in adulthood) Type 2 diabetes, sometimes associated with insulin resistance, is caused by a gradual lack of sufficient β-cell insulin production. Certain forms of diabetes resulting from other causes, such as drug- or chemical-induced diabetes (like glucocorticoid use, HIV/AIDS treatment, or organ transplantation), diseases of the exocrine pancreas (like pancreatitis and neonatal diabetes), and monogenic diabetes syndromes (like neonatal diabetes and maturity-onset diabetes of the young) Diabetes that was discovered in the second or third trimester of pregnancy is known as gestational diabetes mellitus.[2] Among the typical indications and symptoms of diabetes are increased appetite and thirst, urinating often, exhaustion, hazy vision, wounds and cuts heal slowly, numbness or tingling in the hands and feet, recurring infections of the skin, gums, or bladder, Flu-like symptoms, including light-headedness and weakness. The plasma glucose criteria, which include the A1C criteria or the fasting plasma glucose (FPG) or 2-h plasma glucose (2-h PG) values obtained after a 75-g oral glucose tolerance test (OGTT), can be used to diagnose diabetes (Table 1).[3]Diabetic ketoacidosis, hyperosmolar hyperglycemia, or even mortality are examples of acute complications. Cardiovascular illnesses, kidney damage (nephropathy), nerve damage (neuropathy), and eye damage (retinopathy) are examples of serious long-term effects. Foot injury, hypoglycemia, infections, cognitive decline, and gastroparesis. Damage to the peripheral and autonomic nerve systems is the most common consequence of diabetes. The most prevalent kind of diabetic nerve injury is called distal symmetric polyneuropathy, and it often manifests as sensory loss in the lower leg, followed by the upper limb. Early management might halt the course of DPN, therefore prompt diagnosis is essential.[4]Diabetes patients who have diabetic peripheral neuropathy are more likely to develop foot ulcers, which can lead to amputation of the foot and higher death rates. A small percentage of individuals may not exhibit any symptoms at all, while others may exhibit allodynia, hyperalgesia, and pain that is characterized as “burning, electric, and stabbing sensations with or without numbness.”[5]Reduced or absent distal sensation, such as vibration perception with a 128-Hz tuning fork, touch sensation with a 10-g monofilament, thermal discrimination with cold and warm objects, pinprick sensation with a pin, and proprioception, were considered neuropathic signs.[6]Distal symmetric polyneuropathy typically affects the hands and lower limbs, with a “stocking and glove” distribution. A constellation of autonomic neuropathies, such as cardiac autonomic neuropathy, gastrointestinal dysmotility, diabetic cystopathy, and impotence, are among the other diffuse neuropathies that can result from diabetes (Fig.1). Less often, focal neuropathies include peripheral nerve dysfunction that results in isolated mononeuropathies or, less frequently, nerve root dysfunction that results in radiculopathy or polyradiculopathy. (Fig.1)[7]

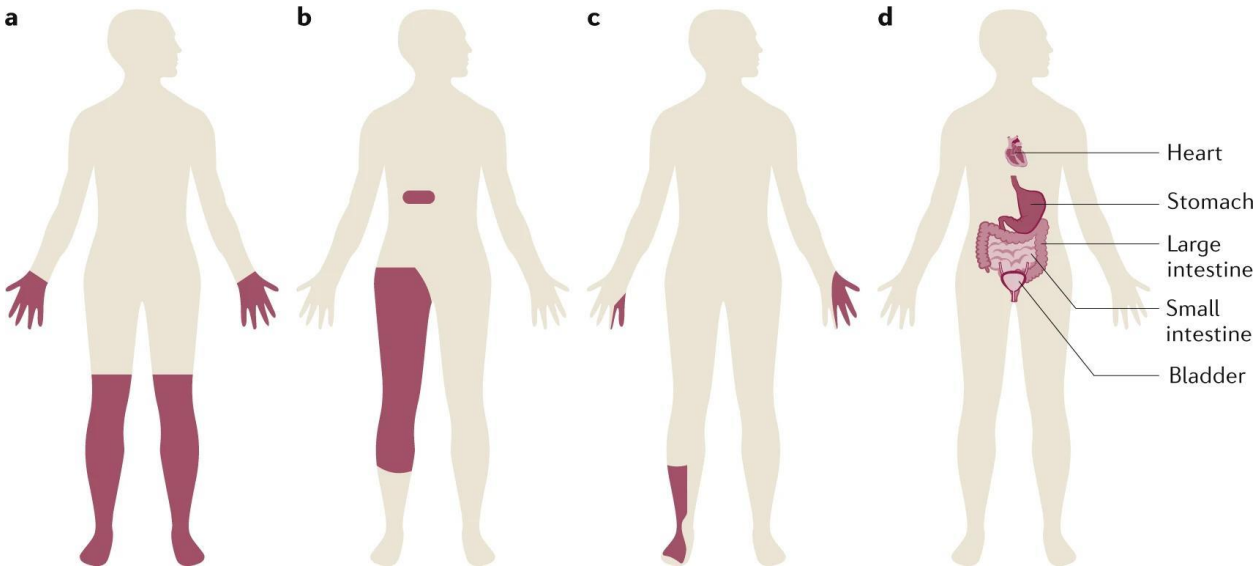

Figure 1: A few instances of neuropathy patterns are DSP, treatment-induced or small-fibre-predominant neuropathy (part a), radiculoplexopathy or radiculopathy (part b), mononeuropathy (part c), and autonomic neuropathy (part d).

According to recent research, SCs are implicated in several DPN development routes. Several important signaling pathways in SCs are triggered during DPN. When these pathways are activated, transcriptional changes follow, which in turn cause sustained increases in ROS production, glycolysis, cellular nicotinamide adenine dinucleotide consumption, and deoxyribonucleic acid (DNA) methylation alterations. These changes ultimately cause diabetic neuropathy, which in turn causes demyelination, axonal conduction abnormalities, impaired neuronal regeneration, and myelin destruction.[8] The four primary risk factors for DPN are insulin resistance, hyperglycemia, dyslipidemia, and microvascular disease. The two most frequent conditions that can initiate the PKC, polyol, AGE, hexosamine, and PARP pathways are hyperglycemia and dyslipidemia.[9].Sorbitol buildup in the axons and Na/K-ATPase malfunction are signs of early neurological impairment. Due to hyperglycemia, aldose reductase (AR) converts excess glucose to sorbitol. A rise in sorbitol has the potential to upset the osmotic equilibrium of cells. Osmotic stress and a corresponding outflow of taurine and inositol follow from this. The typical functional structure of nerve cells is harmed by inositol deficiency. The development of neuropathy is encouraged by the overactivation of the polyol pathway (Figure 2). Oxidative stress is caused by an increase in the generation of reactive oxygen species. Thus sorbitol dehydrogenase turns sorbitol into fructose.[10]

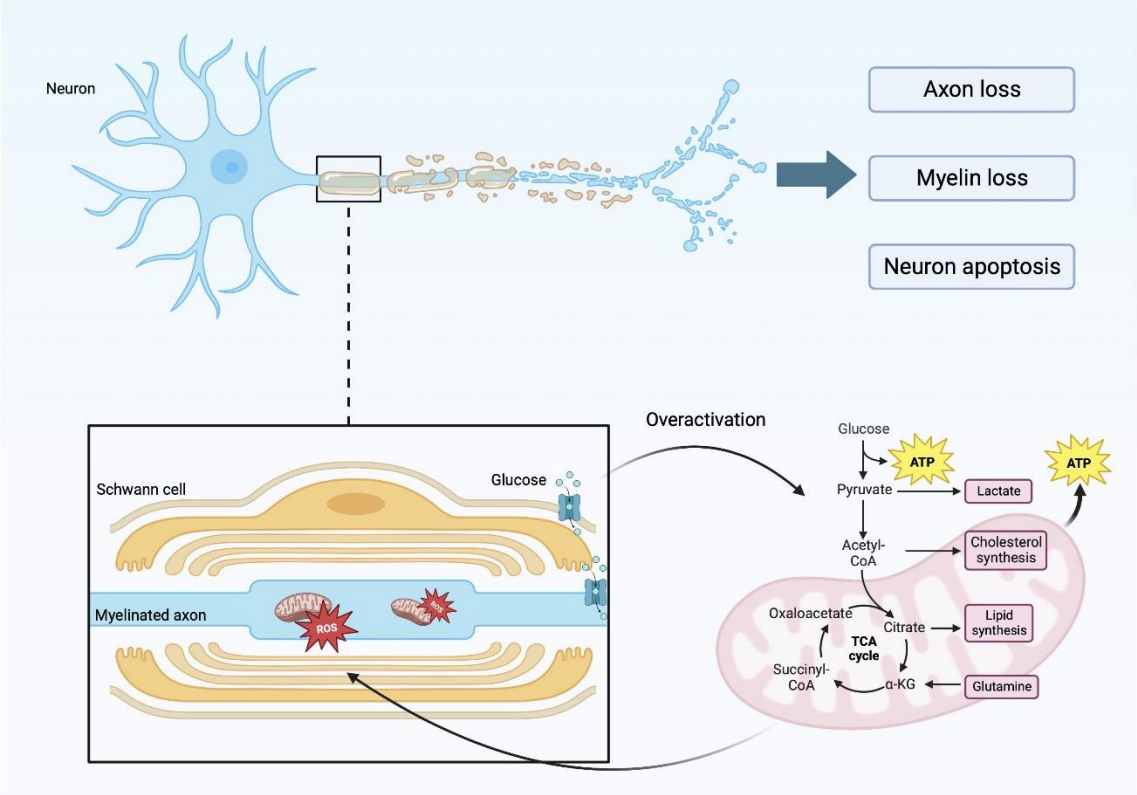

Figure 2: Effect of elevated hbA1c leads to the production of ROS and oxidative stress

However, the pathophysiology of DPN varies noticeably between type 1 and type 2 diabetes. Strict blood glucose control is more effective in preventing the development of DPN in people with type 1 diabetes, while glycemic control alone is less effective in slowing the progression of DPN in people with type 2 diabetes because of the role played by metabolic syndrome-related factors like dyslipidemia and obesity.[11]About 6% of HbA is glycated; HbA1c (5%), with modest contributions from HbA1a and HbA1b (1%), is the major component. Glycation, a nonenzymatic process, causes glucose to covalently attach itself to the N-terminal valine of the hemoglobin β-chain, resulting in HbA1c.[12]HbA1c is a clinically useful measure of the average glycemic state over two to three months. The degree of long-term glycemic variability in diabetes patients has been more widely represented by the fluctuation of HbA1c values from visit to visit over months or years.[13]The American Diabetes Association (ADA) recommends that all diabetes patients' HbA1c readings be kept at 7%. Higher than 7% HbA1c values raise the risk of complications, particularly microvascular problems. The association between HbA1c and blood glucose management in individuals with uncontrolled diabetes was initially documented by Koening and associates. Morbidity can be avoided by detecting diabetic polyneuropathy early.[14]In this research, we will now investigate the effects that high HB A1c levels will have on diabetic peripheral neuropathy.

METHODOLOGY:

This prospective cohort study was conducted in Central Park Medical College and Teaching Hospital Lahore from April 2024 to Dec 2024 on 75 subjects after random collection following the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board (IRB# CPMC/IRB-No/1415) of Central Park Medical College and Teaching Hospital. Verbal informed consent was obtained from all participants before inclusion in the study, and

patient confidentiality was maintained throughout the study. The sample size was calculated using open epi software based on serum HbA1c level with Diabetes mellitus Type 1 (13.9%,n=10) as compared to Diabetes Mellitus Type 2(86.1%,n=62). Using a prospective cohort design and stringent diagnostic criteria. Diabetic patients attending medicine clinics were screened for eligibility. Inclusion criteria were diabetic patients with Type 2 (DM/+DPN group) in the age group 50 ± 10 years and Type 1 in the age group (DM/-DPN group) 20 ± 5 years. The following inclusion criteria were fulfilled: (a) Quantitative studies that allowed for the assessment of a causal association between HbA1c, DPN, and diabetic foot complications; (b) the definition of DPN given in the studies included only sensory neuropathy, not Charcot neuroarthropathy and (c)the study compared HbA1c levels between groups with and without DPN and diabetic foot Complications. Diabetic patients with hypertension, kidney disease, or cardiovascular disease were excluded from the study. At study enrollment, blood samples were collected to measure HbA1c levels. HbA1c levels are calculated by measuring the percentage of hemoglobin that has glucose attached to it. Mass Spectrometry or Capillary Electrophoresis is used to measure HbA1c level.

Results:

A total of 71 patients participated in the quantitative study. The mean age of the patients is 47.45 years. Almost 39 (54.9%) male patients and 32 (45.1%) female patients participated in this study. Among them, 16 (22.5%) were at the young age group, 36 (50.7%) were in the middle age group, and 19 (26.8%) were in the older age group.

Table 1 Demographic Information of the Patients

Factor	Category	n	%
Gender	Male	39	54.9%
	Female	32	45.1%
Age	Young (19 - 37)	16	22.5%
	Middle (38 - 56)	36	50.7%
	Older (>=57)	19	26.8%

Table 2 Association Between Glucose Control (Fasting Glucose Levels and HbA1c) and Peripheral Neuropathy

Factors	Categories	peripheral neuropathy		P-value
		No	Yes	
Fasting Glucose Level (mg/dl)	< 200(mg/dl)	24 (46.2%)	28 (53.8%)	0.001
	> 200(mg/dl)	1 (5.2%)	18 (94.7%)	
HbA1c (%)	Well Controlled Diabetic Patients	13 (81%)	3 (18.7%)	< 0.001
	Poorly Controlled Diabetic Patients	12 (21.8%)	43 (78.2%)	

Table 2 chi-square test results reveal a significant association between fasting glucose levels and peripheral neuropathy (P = .001). In the well-controlled group, 53.8% had peripheral neuropathy, while in the poorly controlled group, 94.7% were affected. This indicates that poorly controlled glucose levels are strongly linked to a higher prevalence of peripheral neuropathy. Patients with poorly controlled glucose are significantly more likely to develop peripheral neuropathy compared to those with well-controlled glucose levels. These findings underscore the importance of maintaining good glucose control to prevent peripheral neuropathy.

The chi-square test results indicate a highly significant association between HbA1c levels and the presence of peripheral neuropathy (P = .000). Among well-controlled diabetic patients, only 18.7% have peripheral neuropathy compared to 78.2% in poorly controlled diabetic patients. This indicates that poorly controlled HbA1c levels are strongly associated with a higher prevalence of peripheral neuropathy. These findings highlight the critical importance of maintaining good HbA1c control to reduce the risk of developing peripheral neuropathy.

Discussion: In the diagnosis, prognosis, and clinical treatment of several chronic illnesses, biomarkers are crucial. Elevated HbA1c measurements may serve as a useful biomarker for the early identification of diabetic peripheral neuropathy in the feet. Reduced HbA1c levels and strict glycemic control are linked to a decline in diabetes complications: a decrease in HbA1c of less than 7% is linked to a 60% decrease in the incidence of peripheral neuropathy (DPN).[15]The relationship between DPN and long-term HbA1c fluctuation in T1D patients is demonstrated by this study. GV may trigger many processes that may raise the risk of DPN, including the overproduction of oxygen-reactive species, an increase in inflammatory cytokines, cell death, and epigenetic modifications. As a result, GV should be a major component of any current glycemic management strategy in addition to HbA1c levels. In a cohort of young individuals with long-standing T1D, Virk et al. Conducted the first investigation into the relationship between HbA1c fluctuation and the development of DPN and cardiac autonomic neuropathy (CAN).[16]Several studies have suggested that HbA1c may show a glycaemic threshold with micro and macrovascular effects of diabetes, indicating that it might be a useful biomarker to identify individuals at risk for different vascular disorders. This study found a strong correlation between an increased prevalence of DPN and HbA1c categories above about 9.0%. The study's findings supported previous reports that indicated a greater frequency of peripheral neuropathy (21.2%) was associated with rising HbA1c categories (≥8%)[17].In turn, oxidative stress may mediate tissue and cell damage through four main molecular pathways: increased flux through the polyol pathway, overproduction of precursors of advanced glycation end products, overactivation of protein kinase C isoforms, and enhanced activity of the hexosamine pathway. Furthermore, fluctuation in HbA1c may potentially increase the expression of a systemic inflammatory marker associated with vascular injury. Cellular metabolic memory, which may not be the same as short-term glycemic variability, is a significant additional mechanism via which HbA1c fluctuation contributes to diabetes problems. A higher impact on metabolic memory compared to prolonged hyperglycemia exposure.[18]Peripheral neuropathy in diabetic feet frequently coexists with other diabetes-related problems. The quality of life of patients with diabetic foot syndrome can be impacted by a variety of factors, including altered gait, psychological complaints, and even disorders. Additionally, men are more likely than women to have diabetic foot impairment, though this has been shown to vary by location.[19]In this study, individuals with peripheral neuropathy who had type 2 diabetes had higher HbA1c levels. Furthermore, we showed that lower conduction velocities in the motor fibers of the Ulnar, Tibial, and Common peroneal nerves as well as in the sensory fibers of the Radial, Median, and Sural nerves are associated with higher levels of HbA1c. These results are consistent

with a recent study that found a relationship between DPN and higher HbA1c levels in diabetic patients.[20]Tight GC (HbA1c 7.1% [54.1 mmol/mol]) in type 2 diabetes protected NCV but not CAN decrease, according to the Kumamoto Study. The effects of intensive and standard GC (HbA1c 7.0% vs. 7.9% [53.0 vs. 62.8 mmol/mol]) on DPN and CAN were similar in the UK Prospective Diabetes Study (UKPDS) (2). The rigorous therapy (HbA1c 6.3% [45.4 mmol/mol]) in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study averted loss of ankle jerk and light-touch feeling, but it also increased total and CVD-related mortality as well as severe hypoglycemia.[21]A meta-analysis was carried out by Liu et al. To investigate the risk markers connected to DN. Documentation from Bangladesh, Kuwait, China, and India was included in the research. This investigation, in line with the present study, discovered that HbA1c is a risk marker for DN.[22]Conversely, people with type 1 and type 2 diabetes are more likely to experience hypoglycemia prevalence when their HbA1c levels are lower. Numerous investigations have indicated an inverse correlation between hypoglycemia and HbA1c in individuals with diabetes.[23]According to a study conducted by Kasper et al., it has been found that extended periods of unregulated high blood sugar levels have been linked to DN as well as other problems affecting micro- and microvasculature.[24]According to research by Ishibashi et al., individuals with type 2 diabetes can postpone the development of microvascular complications including neuropathy and nephropathy by closely monitoring their hbA1c levels.[25]In contrast to individuals with painless neuropathy, Oyibo et al. Found that patients with painful neuropathy had higher glycemic excursions and potentially worse diabetes management in a pilot trial. In the study, we also assessed and contrasted how managing glycemic variability affected the emergence of DPN in individuals with type 2 diabetes under control.[26]A negative correlation between age and HbA1c indicates age-based variations in treatment adherence; that is, the younger the patient, the less adherent they are to their regimen. This is thought to raise glycated hemoglobin levels.[27] The Wagner categorization system, which assesses the extent of the ulcer and the involvement of the bones, is typically used to choose the best course of action and assists in forecasting possible outcomes. In the current study, the great majority of diabetic feet had Wagner Grade 4, which is equivalent to localized gangrene in the heel or forefoot. The development of Wagner Grade 4 diabetic foot was found to be strongly correlated with elevated HbA1c readings. The Wagner grading system and HbA1c readings were correlated, and this was assessed by Farooque et al. 59.08% of the diabetic feet in the study were >8.5%, and the mean HbA1c value of the diabetic feet included in the study was reported to be 9.07%±1.65%.[28]There is a strong correlation between severe infections and poor glycemic control, and HbA1c values are a strong predictor of infection development, according to a 2018 study on the topic of glycemic control and infection risk in patients with Type 1 and Type 2 diabetes.[29]Additionally, we demonstrated that a greater HbA1c level promotes disease severity and tissue loss. Higher hemoglobin A1c values during clinical visits are known to trigger the development of systemic inflammatory response syndrome (SIRS), which poses a life-threatening risk to patients with DFU.[30]In this sector, DPN during the prediabetic stage has gained importance due to observations that patients frequently exhibit small-fiber neuropathy in prediabetes [31]. Thus, future research should examine DPN in prediabetes, including its correlation with HbA1c levels and other variables including smoking, alcohol misuse, and metabolic syndrome at this time.[31]DPN affects up to 50% of diabetics and commonly results in neuropathic pain, foot ulceration, and ultimately amputation[32]The DPN group's median time since the DPC hospital's initial T2DM record was eight months. Given the median length of diabetes in individuals with DPN published in a recent Japanese study (15.9 years)[33] even if it is the period after matching, it appears brief. The real length of diabetes is not often indicated by the definition of this variable, and many the patients in our research group were likely referred from clinics or hospitals that did not specialize in diabetes; as a result, the true duration of T2DM was likely substantially longer.

Conclusion:

According to the study's current findings, there is a substantial correlation between rising HbA1c levels and a higher incidence of DPN, with risk rising noticeably at HbA1c levels ≥8.0%. The longer a person has had diabetes and the older they are, the higher the prevalence and risk of DPN. Patients with diabetes have both long-term and variable glycemic control linked to DPN. If the considerable declines in peripheral neuropathy development continue, they point to the possibility that intensive glucose management may lower ulcer risk and the number of leg amputations in the future, thereby lowering diabetes-related foot complications and considerably enhancing patient quality of life.

Limitations:

It is necessary to acknowledge the limitations of our investigation. Firstly, we did not look at the relationship between endothelial dysfunction, inflammation, oxidative stress markers, and HbA1c variability. Secondly, 8 months is a rather short period for the assessment of HbA1c fluctuation in comparison to several earlier research. Third, the association between DPN severity and HbA1c fluctuation was not assessed. Fourth, instead of doing a neurological examination, we did not employ a particular technique to assess tiny sensory nerve fibers. Furthermore, short-term GV was not assessed. Finally, more extensive statistical modifications were not possible due to the limited sample size.

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