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CORRELATION BETWEEN THE SEVERITY OF DIABETIC PERIPHERAL POLYNEUROPATHY AND GLYCOSYLATED HEMOGLOBIN (HbA1C) LEVELS

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Abstract

Aim: To correlate between the severity of diabetic peripheral polyneuropathy and glycosylated hemoglobin (HbA1C) levels.

Material and method: The present prospective observational study was conducted to evaluate the **type 2 DM with peripheral neuropathy patients from December 2020 to August 2022. 100 subjects** having age > 18 Years, patients diagnosed for DPN by clinically (DNS >=1)/ by electro diagnostic testing (in selected cases) were included in the study. HbA1c levels were assayed using Biochemical method. Severity of DPN Categorized By Neuropathy Disability Score (NDS).

Results: Hypertension and cardiovascular disease was revealed in 14.17% and 6.67% of the subjects respectively. NDS score viz. mild, moderate and severe deficits was found among 13%, 68% and 19% of the subjects respectively. Mean HbA1c level increases along with increase in NDS score i.e., higher the deficits, more is the HbA1c.

Conclusion: It can be concluded that increased HbA1c level indicative of chronic hyperglycemia, could significantly increase the risk and quantitatively reflect the severity of polyneuropathy in diabetic patients.

Keywords: DM, HbA1c, DPN, DNS, Peripheral Neuropathy

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Introduction: Diabetes mellitus (DM) is a metabolic disorder which is characterized by an increased risk of microvascular and macrovascular complications.[1] The prevalence of diabetes

mellitus is growing rapidly worldwide and is reaching epidemic proportions. It is estimated to increase from 4% in 1995 to 5.4% by the year 2025. According to the International Diabetes Federation (IDF) 2013 there are 67.1 million diabetics in India. WHO studies reported total diabetics in India in 2000 was 31.7 million, likely to increase to 79.4 million by 2030.[2]

Diabetic peripheral polyneuropathy (DPN), which includes peripheral nerve damage, is one of the most common complications of DM, affecting approximately 8% of newly diagnosed patients and >50% of patients with long-term DM. It is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in DM patients after exclusion of other possible causes.[3] The prevalence of neuropathy in diabetes patients is approximately 30% in hospital patients and 20% in community patients.[4] DPN is a disease often associated with neuropathic pain, foot ulceration and lower extremity amputation, which can significantly affect the quality of life of patients. The most frequent type of neuropathy associated with diabetic foot complications is the distal symmetric sensorimotor polyneuropathy and along with peripheral vascular disease, it is a major contributing factor to the formation of foot ulcers.[5]

Haemoglobin A1c (HbA1c) is glycated haemoglobin used to monitor the status of glucose levels in the previous 2 or 3 months. Recommendation from the American Diabetes Association (ADA), HbA1c levels must be maintained at 7% in all diabetics patients. HbA1c levels above 7% increase the risk of complications, especially microvascular complications.[6]

Poor glucose control is one of the risk factors that are strongly related to the progression of diabetic neuropathy in patients with type 2 DM. Early screening for symptoms and signs of diabetic neuropathy is important, since it creates a chance to detect the neuropathy at its earliest asymptomatic stages and thus prevent further progression.[6] Many investigators have examined the correlation of HbA1C levels with DM complications. However, very little research has focused on the critical HbA1C level in diabetic peripheral neuropathy. Hence the present study was conducted to correlate between the severity of diabetic peripheral polyneuropathy and glycosylated hemoglobin (HbA1C) levels.

Materials and methods: The present prospective observational study was conducted to evaluate the type 2 DM with peripheral neuropathy patients from December 2020 to August 2022. Informed written consent of all participants was obtained after explaining the purpose of the study. Permission to carry out the study was obtained by institutional ethical committee of CSS Hospital, Subharti Medical College, Meerut. 100 cases (IPD & OPD) with clinical/electrophysiological evidence of DPN were enrolled in the study.

Subjects having age > 18 Years, patients diagnosed for DPN by clinically (DNS >=1)/ by electro diagnostic testing (in selected cases) were included in the study.

Diabetic Neuropathy Symptom Score (DNS) >= 1[7]

DNS Item	**Score**
Unsteadiness in walking	0 = Absent
	1 = Present
Numbness	0 = Absent
	1 = Present

Burning, aching pain or	0 = Absent
Tenderness in legs or feet	1 = Present
Prickling sensation	0 = Absent
	1 = Present

Patient denying consent, patient with other concomitant disease that could cause peripheral neuropathy alcohol abuse, patient with liver disease, renal disease, patient using anticancer drugs, patient using anti-tuberculosis drugs, patient using anti arrhythmic agents, patient with previous brain or spinal cord injury and patient with H/O lumbar or cervical radiculopathy were excluded from the study.

Methodology: Patients diagnosed to have DPN by standard clinical, electrophysiological investigations formed the study group. HbA1c levels were assayed using Biochemical method. Severity Of DPN Categorized by Neuropathy Disability Score (NDS)[8]

NDS:

3-5 = mild deficits

6-8 = moderate deficits

9-10 = severe deficits

Data was collected and subjected to statistical analysis.

Statistical analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). For each assessment point, data were statistically analyzed using one way ANOVA and the level of significance was set at $p < 0.05$. Pearson correlation test was used to analyze correlation between HbA1c and NDS score.

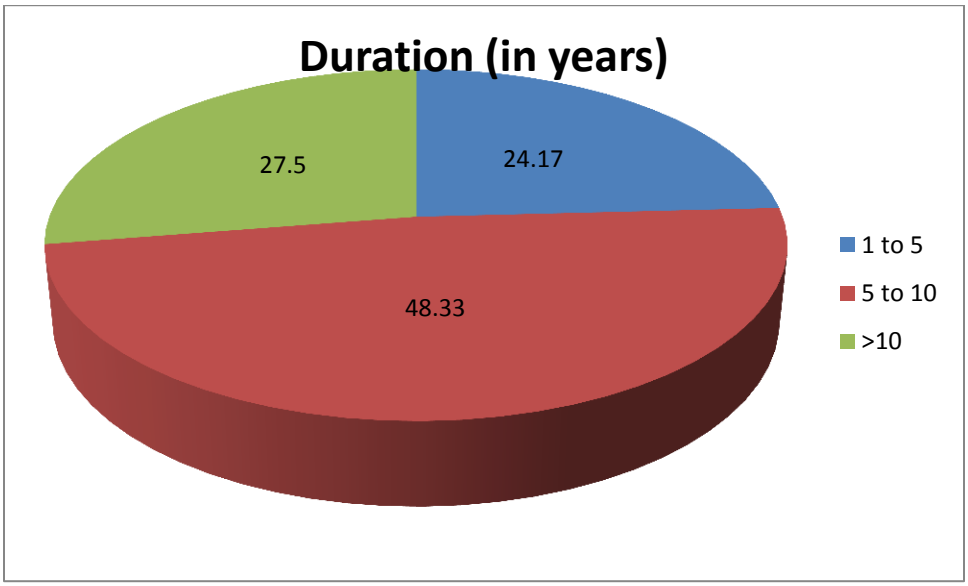
Results: Overall there were 71 males and 49 females. Hence there was slightly more males as compared to females. Most of the subjects in this study were having age >50 years. Mean age among the study subjects was 59.08±12.17 years respectively (table 1).

Table 1: Gender and age distribution among the study subjects

Gender	**N=120**	**%**
Male	71	59.17
Female	49	40.83
Age Group (in years)		
<40	11	9.17
40-49	23	19.17
50-59	51	42.50

>60	35	29.17
Mean±SD	59.08±12.17	

48.33% of the subjects had diabetes for 5-10 years. Approximately 28% of the subjects had diabetes since >10 years (graph 1). Hypertension and cardiovascular disease were revealed in 14.17% and 6.67% of the subjects respectively as shown in table 2.



Graph 1

Table 2: Co-morbidities among the study subjects

Co-morbidities		
Hypertension	17	14.17
Cardiovascular Disease	8	6.67
Other	6	5.00

Mean body weight (kg) among the study subjects was 72.61±5.83. Mean baseline diabetic parameters viz. HbA1c, FBS and PPBS was 8.19±0.44, 184.58±5.08 and 279.13±10.71 among the study subjects. Mean Triglyceride, HDL, LDL and VLDL among the study subjects was 151.76±6.19, 38.28±2.87, 108.11±6.43 and 39.32±3.12 among the study subjects as shown in table 3.

Table 3: BMI and investigations parameters among the study subjects

Variables	**Mean**	**SD**
Body weight (kg)	72.61	5.83
Height (cm)	162.09	4.92
Variables		
HbA1c	8.19	0.44
FBS	184.58	5.08
PPBS	279.13	10.71
Variables		
Triglyceride	151.76	6.19
HDL	38.28	2.87
LDL	108.11	6.43
VLDL	39.32	3.12

NDS score viz. mild, moderate and severe deficits was found among 13%, 68% and 19% of the subjects respectively. Mean NDS score among the study subjects was 7.04±2.36. Mean HbA1c level increases along with increase in NDS score i.e. higher the deficits, more is the HbA1c. When mean HbA1c level was compared according to NDS score using ANOVA test, statistically significant difference was found as $p<0.05$ (table 4).

Table 4: NDS score and mean HbA1c according to NDS score distribution among the study subjects

NDS	**N**	**%**
Mild Deficits (3-5)	13	13
Moderates Deficits (6-8)	68	68
Severe Deficits (9-10)	19	19
Mean±SD	7.04±2.36	

NDS	Mean HbA1c	SD
Mild Deficits (3-5)	7.69	0.21
Moderates Deficits (6-8)	8.06	0.62
Severe Deficits (9-10)	9.58	0.53
Anova test	11.85	
p value	<0.01*	

*: statistically significant

According to Pearson correlation analysis, statistically significant positive correlation was found between HbA1c and NDS score i.e. with increase in HbA1c level, NDS score also increases ($r=0.54$, $p<0.01$) as shown in table 5.

Table 5: Correlation between HbA1c and NDS score

Variables	HbA1c and NDS score
r value	0.54
p value	<0.01*

*: statistically significant

Discussion: In this study, overall, there were 71 males and 49 females. Hence there was slightly more males as compared to females. Most of the subjects in this study were having age >50 years. Mean age among the study subjects was 59.08±12.17 years respectively. In a study by Yun-Ru Lai et al[9], there were 78 women (age range, 35–82 years; mean age, 63.4 years) and 145 men (age range, 29–90 years; mean age, 62.3 years). These findings are similar to our study.

48.33% of the subjects had diabetes for 5-10 years. Approximately 28% of the subjects had diabetes since >10 years. Hypertension and cardiovascular disease were revealed in 14.17% and 6.67% of the subjects respectively. In this study; mean body weight (kg) among the study subjects was 72.61±5.83. Mean baseline diabetic parameters viz. HbA1c, FBS and PPBS was 8.19±0.44, 184.58±5.08 and 279.13±10.71 among the study subjects. Mean Triglyceride, HDL, LDL and VLDL among the study subjects was 151.76±6.19, 38.28±2.87, 108.11±6.43 and 39.32±3.12 among the study subjects. Yun-Ru Lai et al[9] in their study too mentioned that those with higher SD-HbA1c values had higher body weight ($P = 0.04$) and body mass index ($P = 0.004$), higher mean and index HbA1c values ($P < 0.0001$ and $P <0.0001$, respectively), higher triglyceride and uric acid levels ($P < 0.001$ and $P < 0.0001$, respectively), higher urinary albumin excretion (mg/day), higher albumin-creatinine ratio (mg/mg) ($P = 0.008$ and $P = 0.002$,

respectively), lower eGFR (P < 0.0001), higher prevalence of hypertension and metabolic syndrome as the underlying disease.

NDS score viz. mild, moderate and severe deficits was found among 13%, 68% and 19% of the subjects respectively. Mean NDS score among the study subjects was 7.04±2.36. Mean HbA1c level increases along with increase in NDS score i.e., higher the deficits, more is the HbA1c. When mean HbA1c level was compared according to NDS score using ANOVA test, statistically significant difference was found as $p<0.05$. According to Pearson correlation analysis, statistically significant positive correlation was found between HbA1c and NDS score i.e., with increase in HbA1c level, NDS score also increases ($r=0.54$, $p<0.01$) in this study.

Similarly Won-Jae Lee et al[10] in their study revealed that HbA1c level was a quantitative indicator of the severity of polyneuropathy; and poor glycemic control (HbA1c level >6.5%) could increase the risk for the concurrence of polyneuropathy in DM patients by more than 5-fold. According to Nathan DM[11], the measurement of high levels of HbA1c could be a strategic biomarker to detect diabetic foot peripheral neuropathy. Indeed, intensive glycemic control and lower levels of HbA1c are followed by a reduction in diabetic complications: in HbA1c, <7% is associated a 60% reduction in the incidence of peripheral neuropathy.

In a study by Ilsa Hunaifi et al[12], the median NDS score is 7.5 and the median HbA1c value is 8.65. Spearman correlation analysis shows a correlation coefficient of 0.487 with a value of $p = 0.000$. They concluded that there is a relationship between HbA1c level and the severity of diabetic neuropathy in Type 2 DM. Zilliox et al[13] research showed that NDS values in DM neuropathies were 6.26 (SD 0.34). The electrodiagnosis examination found in patients with large fiber neuropathy showed a heavier NDS value compared to patients with small fiber neuropathy [(7.23 (SD 0.91) vs 4.77 (SD 0.53)]. The research of Stem et al[14] showed that complications of DM (neuropathy, retinopathy, or nephropathy) occur in patients with HbA1c 8.5 (SD 1.5). The higher levels of HbA1c will further accelerate and worsen the complications of neuropathy. Control of glucose levels is very important to prevent and decrease the complications from DM. High levels of HbA1c have associated with high microvascular complications in people with DM.

The use of HbA1c level as an indicator of the severity of polyneuropathy and poor glycemic control (HbA1c level >6.5%) could significantly increase the risk and quantitatively reflect the severity of polyneuropathy in diabetic patients. Evidence suggests that a high level of HbA1c can lead to diabetic peripheral neuropathy, so patients with high levels of HbA1c should be considered to be at the potential risk of diabetic foot complications—foot ulcerations or injuries—that frequently occur in DPN and should receive preventive education from a podiatrist.[10,14]

The limitation of the present study is its cross-sectional design along with small sample size.

Conclusion: HbA1c level is related to the severity of neuropathy in patients with type 2 diabetes as assessed by clinically (DNS >=1)/ electro-physiological testing. The higher the HbA1c value,

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the higher the Neuropathy Disability Score. Monitoring of HbA1c level is crucial to prevent further complications of DM both in the nervous system and in other organs.

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