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A Study of The Correlation between Hba1c and Neuropathy Disability Score in Diabetic Patients

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ABSTRACT

Background: Diabetes mellitus is associated with chronic complications, among which is peripheral neuropathy. The severity of diabetic peripheral neuropathy (DPN) is evaluated using the Neuropathy Disability Score (NDS). Hemoglobin A1c (HbA1c) is a measure of glycated hemoglobin utilized to monitor diabetic patients' glucose levels over the past 2 or 3 months. DPN is linked to glycemic exposure and the duration of diabetes. However, evidence suggests that only rigorous glycemic control, monitored by HbA1c levels, can alleviate or prevent neuropathy.

Objectives: This study aimed to examine the correlation between HbA1c and the neuropathy disability score in a specific group of participants. Additionally, the research explored the potential impact of various demographic and clinical factors on this correlation.

Patients and Methods: This cross-sectional study encompassed 198 adult subjects diagnosed with type 2 DM who sought medical care at the Neurology and Internal Medicine Departments of Benha University Hospital in Egypt between July 2021 and July 2022. All participants underwent medical history assessments, general and neurological examinations, HbA1c tests, lipid profile evaluations, liver function tests, kidney function assessments, and a revised neuropathy disability score to identify signs of neuropathy.

Results: The Neuropathy Disability Score (NDS) exhibited a significant correlation with HbA1c % and various factors, including age, BMI, blood pressure (SBP and DBP), fasting blood sugar (FBS), serum creatinine, LDL-C, HDL-C, and the duration of diabetes. However, it does not display significant correlations with triglyceride levels or total cholesterol.

Conclusion: A strong correlation exists between HbA1c levels and the presence of diabetic neuropathy.

Keywords: Diabetic peripheral neuropathy (DPN), Neuropathy Disability Score (NDS), HbA1c.

INTRODUCTION

Diabetes mellitus arises from a metabolic disorder involving defects in insulin secretion, insulin action, or both [1]. Projections suggest that by 2030, approximately 360 million individuals will have diabetes [1, 2]. This condition can lead to enduring complications, such as retinopathy, nephropathy, neuropathy, and other vascular issues [3].

Diabetic peripheral neuropathy (DPN) is among the most prevalent microvascular complications in both type 1 and type 2 diabetes. DPN is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in individuals with diabetes after excluding other causes"[4]. It can predispose individuals to foot ulceration and gangrene, elevating the risk of non-traumatic amputation [5]. Moreover, DPN is closely linked to alterations in brain structure, notably a decrease in peripheral grey matter volume, potentially contributing to walking impairments [6, 7].

Consequently, patients affected by DPN might experience a diminished quality of life and face substantial costs for diabetes care [8]. The fundamental pathogenesis of DPN remains a topic of debate [9]. Research indicates associations between DPN and factors such as glycemic exposure, duration of diabetes, insulin resistance, visceral adiposity, dyslipidemia, and hypertension [9]. Microvascular complications of diabetes might be linked to inadequate time-dependent glycemic control [10].

Additionally, glycemic variability is now acknowledged as an indicator of compromised glycemic control, potentially predicting diabetic complications [11, 12]. Therefore, assessing long-term glycemic variability through variations in HbA1c over several months could serve as a reliable risk factor for microvascular complications, including diabetic neuropathy. **Jun *et al.*** [13] have shown a significant association between HbA1c variability and the presence as well as severity of cardiovascular autonomic neuropathy (CAN) in type 2 diabetic patients. However, the role of HbA1c variability in DPN remains less understood. Thus, we conducted a study to evaluate the relationship between long-term glycemic variability, assessed by HbA1c fluctuations, and DPN in patients with type 2 diabetes.

PATIENTS AND METHODS

Study Design: This was a cross-sectional study of adult patients who visited the Neurology and Internal Medicine Departments, in Benha University Hospital, Egypt from July 2021 to July 2022. **Data Collection:** A total of 198 adult patients diagnosed with type 2 diabetes mellitus (DM) were included in this study. The sample size "n" was determined using the Cochran formula.

Cochran formula is: $n = Z^2pq/e^2$

Where e is the desired level of precision (i.e., the margin of error). P is the estimated proportion of the population, which has the attribute in question is 1-p.

Inclusion criteria: Cases with type 2 diabetes mellitus, adult males and females were included.

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Exclusion criteria: Patients with type 1 DM, hereditary neuropathy, renal or hepatic impairment, inflammatory or autoimmune diseases

For all subjects the following were recorded:

Demographic Information: Age, sex, and smoking status were documented.

Type 2 Diabetes Diagnosis: Diagnosis was established based on the criteria outlined in the American Diabetes Association (ADA) statement of 2021 [14]. Laboratory results from venous blood samples, collected after an overnight fasting period of at least 8 hours, were examined for fasting plasma glucose, 2-hour postprandial plasma glucose, and HbA1c. Diabetes was defined as fasting plasma glucose levels ≥ 126 mg/dL, 2-hour postprandial plasma glucose levels ≥ 200 mg/dL, or HbA1c levels ≥ 6.5%.

Blood Pressure Readings: Systolic and diastolic blood pressure readings were taken while subjects were in a supine position following a 10-minute rest. Individuals were categorized as having hypertension if their blood pressure was at or above 130/80 mmHg, and as not having hypertension if it was below 130/80 mmHg, in accordance with the 2017 ACC/AHA hypertension guideline recommendations.

Body Mass Index (BMI): Participant weight (in kilograms) was measured using a calibrated digital scale, and height (in centimeters) was assessed with a stadiometer. BMI was calculated using the formula: BMI = weight (kg) / (height (m^2). Reference values for normal BMI range between 18.5 - 24.9 kg/m^2 [15].

Lipid Profile: Dyslipidemia was defined as having a total cholesterol level >200 mg/dL, triglyceride level >180 mg/dL, serum high-density lipoprotein cholesterol (HDLC) <40 mg/dL in men and <50 mg/dL in women or having a prescription for low HDL-C levels or lipid-lowering medication as per the AHA guidelines at the time of the study.

Assessment of Revised Neuropathy Disability Score (NDS):

The evaluation aims to assess neuropathic signs, incorporating various criteria:

Ankle reflex: Normal = 0, Present with reinforcement = 1, Absent = 2 per side.

Sensory tests include vibration sensation using a 128 Hz tuning fork, pinprick, and temperature sensation (Cold tuning fork). A score of 0 indicates normal sensation, while a score of 1 signifies reduced or absent sensation on both sides of the great toes, with a maximum achievable score of 10 points. Individuals scoring six points or more on the NDS are deemed to exhibit abnormal reactions [16-18].

Severity Grading of Neuropathy:

The severity levels are categorized as follows: Mild (scores: 3–5), Moderate (scores: 6–8), and Severe (scores: 9–10) [19, 20].

Ethical Consent:

The Academic and Ethical Committee of Benha University granted approval for the project (Rc 4-6-2022). Each participant provided written informed consent before participating, aligning with the Helsinki Declaration.

Statistical Analysis

SPSS version 20 for Windows was utilized for all statistical computations. Descriptive statistics were used to present demographic details and collected data, including mean ± standard deviation (SD) for quantitative data, and frequency distributions for qualitative data. Student's t-test was applied to compare means of two groups of quantitative data and chi^2 test was used to compare qualitative data. The correlation coefficient was utilized to identify relationships between variables. The Pearson correlation coefficient was specifically employed to identify relationships between variables, including the NDS and other parameters. In the analyses, a P value <0.05 was considered statistically significant and a P value <0.01 was regarded as highly significant in all analyses.

RESULTS

Table 1 shows a comprehensive overview of the demographic and medical characteristics observed in the study. Out of the 198 individuals, 64.1% were female. Of the total, 30.3% were smokers. Regarding medication usage, 39.4% used insulin, and 60.6% utilized oral anti-diabetic (OAD) medications. Notably, all participants exhibited microvascular complications. The average duration of diabetes among the sample is 11.18 years.

Table (1): Participant characteristics:

	No (198)	%
Sex Male Female	 71 127	 35.9 64.1
Smoking Yes No	 60 138	 30.3 69.7
Medications Insulin OAD	 78 120	 39.4 60.6
Microvascular comp Yes No	 198 0	 100 0.0
Duration (years) Mean Sd range	11.18 6.08 2-25	

OAD: oral anti-diabetic, SD: standard deviation.

The Neuropathy Disability Score (NDS) demonstrated significant correlations with several factors, such as BMI, blood pressure (SBP and DBP), fasting blood sugar (FBS), serum creatinine, LDL-C, HDL-C, duration of diabetes, and HbA1c%. Notably, it did not exhibit significant correlations with triglyceride levels or total cholesterol **(Table 2)**.

Table (2): Correlation between NDS and other variables among the studied group:

NDS	Pearson correlation (r)	P value
BMI (Kg/m^2)	0.147	0.039*
SBP (mmHg)	0.338	<0.001**
DBP (mmHg)	0.533	<0.001**
FBS (mg/dL)	0.316	<0.001**
S creatinine (mg/dL)	0.261	<0.001**
TG level (mg/dL)	-0.01	0.886
LDL-C (mg/dL)	0.230	0.001**
HDL-C (mg/dL)	-0.361	<0.001**
Total-C (mg/dL)	-0.01	0.886
Duration	0.751	<0.001**
HbA1c %	0.512	<0.001**

*: Significant, **: Highly Significant

There were significant differences in the mean NDS across different groups. Specifically, males, smokers, and insulin users exhibited higher NDS scores, whereas non-smokers and individuals using OAD medications showed lower NDS scores. These distinctions were statistically significant, supported by the associated p-values **(Table 3)**.

Table (3): Correlation between mean NDS and other variables among the studied group:

		Mean NDS	±SD	Mann-Whitney test	P-value
Sex	Male (71)	7.24	1.89	2.65	0.009**
	Female (127)	6.43	2.16		
Smoking	Yes (60)	7.17	2.09	2.0	0.047*
	No (138)	6.52	2.08		
Medications	Insulin (78)	8.1	1.47	8.81	<0.001**
	OAD (120)	5.82	1.96		

*: Significant, **: Highly Significant

Sex, smoking habits, and medication usage exhibited statistically significant associations with the levels of NDS (Neuropathy Disability Score). Regarding sex, a notable difference emerged: more females were observed in the "Mild" and "Moderate" NDS levels, while more males fell into the "Severe" category. Smoking also demonstrated a significant correlation, as smokers tended to align with the "Mild" NDS category, while non-smokers were more prevalent in the "Severe" category. Insulin users showed a higher likelihood of having a "Severe" NDS, whereas OAD users were more inclined towards a "Mild" NDS. However, age did not display a statistically significant difference across NDS categories. Nevertheless, there were notable contrasts in the mean duration of diabetes and HbA1c levels. Individuals within the "Severe" NDS category showcased longer durations of diabetes and higher HbA1c levels in comparison to those in the "Mild" or "Moderate" categories **(Table 4)**.

Table (4): Correlations of Neuropathy Disability Score (NDS) with demographic and medical factors

NDS	**Mild (37)**		**Moderate (134)**		**Severe (27)**		**Statistical test**	**P value**
	No	**%**	**No**	**%**	**No**	**%**		
Sex								
Male	**8**	**21.6**	**48**	**35.8**	**15**	**55.6**	**X^2= 7.82**	**0.02***
Female	**29**	**78.4**	**86**	**64.2**	**12**	**44.4**		
Smoking								
Yes	**27**	**73.0**	**99**	**73.9**	**12**	**44.4**	**X^2= 9.45**	**0.009****
No	**10**	**27.0**	**35**	**26.1**	**15**	**55.6**		
Medications								
Insulin	**0**	**0.0**	**55**	**41.0**	**23**	**85.2**	**X^2= 47.92**	**<0.001****
OAD	**37**	**100**	**79**	**59.0**	**4**	**14.8**		
	Mean	**Sd**	**Mean**	**Sd**	**Mean**	**Sd**	**Kruskal-Wallis test**	**P value**
Age	**54.3**	**9.44**	**55.83**	**7.06**	**59.19**	**11.31**	**2.85**	**0.06**
Duration	**4.03**	**1.88**	**11.65**	**4.45**	**18.63**	**6.48**	**86.51**	**<0.001****
HbA1c	**7.26**	**0.55**	**8.10**	**1.05**	**9.16**	**2.02**	**20.72**	**<0.001****

*: Significant, **: Highly Significant

In this multiple linear regression analysis, several predictor variables exhibited significant associations with NDS. BMI (Kg/m²), DBP (mmHg), and FBS displayed positive associations, suggesting that higher values of these variables correlate with higher NDS scores. Moreover, there was a positive association between NDS and HbA1c levels. However, SBP (mmHg), LDL-C, HDL-C, and total-C did not demonstrate statistical significance **(Table 5)**.

Table (5): Linear regression to detect the independent predictor of NDS.

NDS %	B	P value	95%CI
BMI (Kg/m^2)	0.023	<0.001**	-0.01-0.035
SBP (mmHg)	-0.004	0.341	-0.012-0.004
DBP (mmHg)	0.04	<0.001**	0.024-0.056
FBS	0.022	<0.001**	0.02-0.024
LDL-C	0.002	0.685	-0.009-0.014
HDL-C	0.01	0.126	-0.003-0.022
Total-C	-0.003	0.263	-0.009-0.002
NDS	0.094	<0.001**	0.055-0.133
r^2	0.881		
Adj r^2	0.876		
F	174.9		
P value	<0.001**		

**: Highly Significant

DISCUSSION

Diabetic peripheral neuropathy (DPN) stands as the most prevalent complication of diabetes, leading to physical disability and profoundly affecting the quality of life, morbidity, and mortality rates [21]. This study aimed to assess the correlation between HbA1c levels and neuropathy disability scores among a specific group of participants at Benha University Hospital. The findings demonstrated a notably strong and significant relationship between HbA1c levels and the presence of diabetic neuropathy. These results align with prior research, notably the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial [22], which highlighted the pivotal role of intensive diabetic control—defined by an HbA1c level of 6.3%—in preventing neuropathic deficits such as the loss of ankle jerk and light-touch sensation [23, 24].

Moreover, the UKPDS (United Kingdom Prospective Diabetes Study) emphasized a direct connection between elevated HbA1c levels in individuals with diabetes mellitus and an escalated risk of complications [25, 26]. These compelling outcomes were supported by another study, showcasing a correlation between HbA1c levels and nerve damage. Significantly, patients with HbA1c levels equal to or greater than 8 had a 3.13 times higher risk of experiencing nerve damage [25, 27]. Additionally, it was observed that each 1% increase in HbA1c levels correlated with a 10-15% higher frequency of diabetic neuropathy [28].

To gain a more comprehensive understanding of the factors influencing neuropathy, a regression analysis assessed the impact of independent variables on the Neuropathy Disability Score (NDS). This analysis identified HbA1c as a significant predictor of neuropathy as evaluated by the NDS score. These findings underscore the critical importance of maintaining optimal glycemic control to mitigate the risk of diabetic neuropathy [28].

In addition to exploring the relationship between HbA1c levels and neuropathy, this study investigated potential links between neuropathy and various demographic factors, such as sex and age and other disease-related factors such as diabetes duration, and type of therapy. The analysis did not find any statistically significant difference in NDS categories related to age, consistent with prior research suggesting that age might not play a significant role in the development of diabetic neuropathy[25, 29].

However, our study observed a gender-based difference, with males exhibiting higher NDS scores. This finding contrasts with an earlier study that concluded there was no statistically significant connection between sex and the occurrence of neuropathy [25, 29].

Additionally, our study demonstrated that the duration of diabetes and the type of therapy used played significant roles in the severity of neuropathy. Patients with a longer duration of diabetes and those on insulin therapy showed more severe neuropathy [30]. This aligns with other clinical studies reporting a lower prevalence of polyneuropathy in individuals with a diabetes duration of less than 5 years and a higher prevalence in those with a diabetes duration of more than 15 years [28] and those on insulin therapy [30]. Our study revealed significant associations between NDS and several predictor variables such as BMI (Kg/m²), DBP (mmHg), and FBS (mg/dL), which are consistent with the findings of a previous study. This prior research reported that DPN is associated with elevated body mass index, hypertension, and dyslipidemia [9, 21].

Several limitations are important to note in this study. Firstly, its single-center nature may restrict the generalizability of findings to broader populations. Secondly, while the study investigated the impact of demographic factors like gender and age on neuropathy, it did not extensively examine other potential variables contributing to neuropathy risk, such as socioeconomic status, education, and race. Thirdly, due to the cross-sectional design, temporal relationships couldn't be thoroughly assessed, warranting the need for future longitudinal studies. Lastly, the absence of intervention data limits insights into understanding the effects of diabetes management on neuropathy outcomes.

CONCLUSION

This study emphasizes the strong correlation between HbA1c levels and the presence of diabetic neuropathy. Moreover, the influence of demographic factors and therapy type on neuropathy severity underscores the need for personalized approaches to

diabetes management. These findings contribute to the expanding body of knowledge on diabetic neuropathy and reinforce the significance of glycemic control in mitigating the risk of complications.

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