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SEVERITY OF PERIPHERAL DIABETIC NEUROPATHY WITH BIOCHEMICAL AND DOPPLER STUDIES

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Abstract

Objective: *To measure the severity of diabetic neuropathy with biochemical and doppler studies in diabetes-type II patients who never complained of peripheral neuropathy.*

Study design: *Descriptive study*

Place and duration of study: *Department of Internal Medicine Fazaia Ruth Pfau Medical College (FRPMC), PAF Base Faisal, Karachi. The duration was six months.*

Methodology: *After seeking permission from the ethical committee of our hospital, our hospital performed our research with a sample of 135 patients who were subjected to biochemical and doppler studies. The biochemical studies involved glomerular filtration rate and serum cholesterol level and doppler studies involved a novel index pedal acceleration time. The severity of neuropathy (vasculopathy) was based on pedal acceleration time, and we compared it to the glycemic derangements among patients. The demographics were also recorded.*

Results:

The primary outcome was the severity of vasculopathy among diabetic patients. Sixty-four (47.4%) patients had mild vasculopathy, 46 (34.1%) patients had moderate vasculopathy and 25 (18.5%) patients had critical vasculopathy. Five patients (20.0%) with mild glycemic derangement had critical vasculopathy, 5 (20.0%) patients with moderate glycemic derangement had critical vasculopathy and 15(75.0%) patients with severe glycemic derangement had critical vasculopathy with p value of 0.001.

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Conclusion: *We concluded doppler studies based on pedal acceleration time correlate with the severity of glycemic control. GFR did not correlate significantly with neuropathy severity, but serum cholesterol levels correlated with severity of neuropathy.*

INTRODUCTION

Diabetes is a global epidemic, and it has erupted into another epidemic of complications in which diabetic polyneuropathy is the most prevalent. Greater than fifty percent of individuals with diabetes develop polyneuropathy especially in uncontrolled diabetes and leads to sinister complications like non-traumatic amputations and silent myocardial infarctions. About seventy percent of diabetics suffer from either clinical neuropathy or subclinical neuropathy.[2] It is a grim complication which leads to morbidity, mortality, and massive economic strain in resource limited countries like Pakistan.

Pakistan has sixth highest prevalence of diabetes in the world and every fourth individual is vulnerable to diabetes due to obesity, which is alarming.[3] Over five lac Pakistani diabetic patients lost their limbs in year 2022. This high rate of amputation has resulted in an enormous resource burden in terms of loss of productivity, costs of rehabilitation, transport, disability, and treatment.[4] According to a survey by Tazeen H Jafar et al, Pakistan can achieve twenty percent reduction in mortality and economic costs by risk factor reduction.[5] Many patients with diabetes are oblivious to diabetic neuropathy, which is back drop of these complications. People living in rural areas have limited access to good healthcare facilities and preventive measures.[6] Early identification of peripheral neuropathy and peripheral vascular disease in asymptomatic patients is essential for limiting the progression into complications creating a window of opportunity for optimization and reduce morbidity and mortality and economic costs of the disease.[7]

In this study we will measure frequency of biochemical derangements and vasculopathy in diabetic patients who were seemingly asymptomatic. We will use a novel duplex technique to detect foot perfusion to detect severity of vasculopathy. This study will help us to identify patients who are at risk of developing higher grades of diabetic neuropathy so that we can start timely treatment and prevent progression to advance stages of disease.

Methodology:

After seeking permission from the ethical committee of our hospital we performed our research at the department of internal Medicine Fazaia Ruth Pfau Medical College (FRPMC), PAF Base Faisal, Karachi. The duration of our study was six months. The sample was calculated with WHO sample size calculator with 5% level of significance and 90% power of test. The pedal acceleration time (PTA)of non-ischemic plantar arteries to be 20 milli second[8] and pedal acceleration time (PTA) of mild ischemic arteries to be 120[8] milliseconds. The minimum sample size came out to be 135. We employed non-probability consecutive sampling technique to gather samples after application of inclusion and exclusion criteria. **Inclusion criteria**: We included all type-II diabetic patients of both genders of any age established as per American Diabetes Association (ADA) guidelines with 10 years history of diabetes mellitus who came for routine check-up in medical outpatient department and had Toronto Clinical Scoring System (TCSS) 0-5.[9] The patients who agreed to participate, and follow-up voluntarily were included in the study. **Exclusion criteria:** Patients (aged between 20-70 years) diagnosed with diabetic neuropathy with history of amputation, plantar fasciitis, foot infection, lumbar spinal stenosis, athlete's foot or foot ulcer, B12 deficiency, thyroid disorders and Rheumatoid Arthritis were excluded. Patients who smoked cigarettes and had history of ischemic heart disease were also excluded.

The patients were advised following biochemical investigations: Serum HBA1c, eGFR and serum total cholesterol. They were subjected to a novel method of measurement of ischemia using non-invasive duplex ultrasound of pedal arteries by an experienced radiologist. Duplex imaging of the pedal arteries was carried out in radiology department with patients in supine position. Pedal acceleration time (PAT)[10] was measured using a linear array transducer with Doppler frequencies ranging from 3 to 12 MHz.

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measurements from four PAT sites were made which include arcuate artery, medial plantar artery, lateral plantar artery, and deep plantar artery. After adjusting the color scale and direction, doppler was applied at center of artery to get a live spectral waveform. The waveform be frozen and Pedal acceleration time (PAT) was measured with help of tool for calculation of time slope in milliseconds. The PAT was measured from the beginning of the up-rise of systole to the peak of systolic up-stoke.[9] The patients who were follow-up with the biochemical and doppler studies will be included in the study. The following parameters were recorded: Mild glycemic derangement (HBA1c 7-8), moderate glycemic derangements (HBA1c 9-10), severe glycemic derangement (HBA1c >11), estimated glomerular filtration rate (eGFR) and serum cholesterol. The severity of vasculopathy of pedal arteries was based on Pedal acceleration time (PAT). Pedal acceleration time (PAT) of 121-180 milliseconds will be labelled as mild vasculopathy, Pedal acceleration time (PAT) of 181-224 were labelled as moderate vasculopathy and Pedal acceleration time (PAT) of greater than 225 milliseconds were labelled as critical vasculopathy. The following demographic features were recorded: age group, gender, weight, height and BMI. Comorbid conditions like obesity and hypertension were also recorded.

The data was analyzed using Statistical Package of Social Sciences (SPSS). The qualitative variable were analyzed through frequency and percentages. Quantitative variables were analyzed using means and standard deviation. Chi-square analysis was used to compare frequencies. P value less than 0.05 will be considered significant. An independent sample T-test was used to compare quantitative variables.

Phases of the study: Enrollment, follow-up and analysis in Figure-I

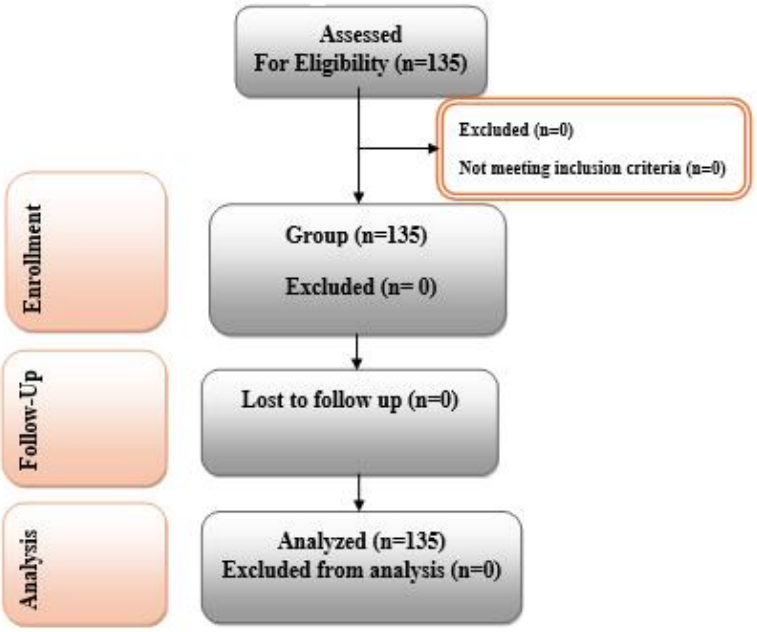

Figure-I: consort diagram of phases of study

Results:

We recruited 135 patients in the study. There were 106 (78.5%) males and 29 (21.5%) females in the study group. Three patients (2.2%) had age between 20-30 Years, 6 (4.4%) patients had age between 31-40 Years, 35 (25.9%) patients had age between 41-50 Years and 46 (34.1%) had age between 61-70 Years. The mean weight of patients was 69.34±5.03Kg, mean height was 162.02±11.05 cm and mean basal metabolic index was 27.03±2.84 (Kg/m^2) as seen in Table-I.

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The primary outcome was the severity of vasculopathy among diabetic patients. Sixty-four (47.4%) patients had mild vasculopathy, 46 (34.1%) patients had moderate vasculopathy and 25 (18.5%) patients had critical vasculopathy (Table-II). Five patients (20.0%) with mild glycemic derangement had critical vasculopathy, 5 (20.0%) patients with moderate glycemic derangement had critical vasculopathy and 15(75.0%) patients with severe glycemic derangement had critical vasculopathy with p value of 0.001. The frequency of hypertension was 5 (20.0%) in patients with critical vasculopathy, it was 11 (23.91%) in patients with moderate vasculopathy and 15 (23.43%) had mild vasculopathy with p value of 0.07. Three obese patients (12.0%) had critical vasculopathy, 5 (10.86%) obese patients had moderate vasculopathy and 17 (26.56%) patients had mild vasculopathy with p value of 0.923 (Table-III). The mean glomerular filtration rate was similar in all three categories of vasculopathy with p value of 0.212. The mean cholesterol levels showed significant association with severity of vasculopathy with 157.04±2.93mg/dl cholesterol in mild vasculopathy, 161.32±6.32 mg/dl of cholesterol in moderate vasculopathy and 168.92±8.35 in critical vasculopathy with p value of 0.001. (Table-IV).

Table-I: The demographic characteristics of the study group (n=135)

Parameter		
Frequency Of Age Groups	20-30 Years	3(2.2)
	31-40 Years	6 (4.4)
	41-50 Years	35 (25.9)
	51-60 Years	45 (33.3)
	61-70 Years	46 (34.1)
Gender	Male	106 (78.5)
	Female	29 (21.5)
Mean Weight (Kg)		69.34±5.03
Mean Height (cm)		162.02±11.05
Mean BMI (Kg/m^2)		27.03±2.84

Table-II: Frequency of different categories of vasculopathies in the study group on basis of Pedal acceleration time (PAT) (n=135)

Vasculopathy	Frequency (%)
Mild	64 (47.4%)
Moderate	46 (34.1%)
Critical	25 (18.5%)

Table-III: Comparison of frequency of different vasculopathy grades among categories of glycemic derangements (n=135)

Glycemic derangement	Mild vasculopathy	moderate vasculopathy	Critical vasculopathy	p value
Mild	56 (87.50%)	12 (26.08%)	5 (20.0%)	0.000
Moderate	8 (12.50%)	30 (65.21%)	5 (20.0%)	
Severe	0(0%)	4 (8.69%)	15 (75.0%)	

Table-IV: The comparison of comorbid conditions with respect to vasculopathy (n=135)

		Mild vasculopathy	moderate vasculopathy	Critical vasculopathy	p value
Hypertension	Yes	15 (23.43)	11 (23.91)	5 (20.0)	0.07
	No	49 (76.56)	35 (76.08)	20 (80.0)	

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Obesity	**Yes**	17 (26.56)	5 (10.86)	3 (12.0)	0.923
	No	47 (73.43)	41 (89.13)	22 (88.0)	
Mean eGFR		82.20 ±1.92	82.72±2.64	82.68±3.83	0.212
Mean Cholesterol		157.04±2.93	161.32±6.32	168.92±8.35	<0.001

Discussion:

We were able to establish that vasculopathy sets in early before the symptoms of neuropathy manifest themselves in the form of complication therefore, we can use it for identification of patients at risk and can help them with timely interventions. The severity of vasculopathy correlated with glycemic derangements. The glomerular filtration rate was on lower side of normal but similar among all groups, but cholesterol levels showed significant variation among the categories of vasculopathy based on severity. Vasculopathy is the hallmark of diabetic neuropathy according to R. A. Malik nerve capillaries are more vulnerable to damage compared to skin and muscles. They advocated that basement membrane of nerve capillaries showed increased thickness with decreased diffusing capacity of oxygen. They were able to establish that vasculopathy correlated well with neuropathological degree of severity of neuropathy.[11]

Diabetic foot is a very important and stressful complication of diabetes and screening is very important to prevent it. Supervision of glycemic control is important but screening for high-risk population should be done to prevent this cumbersome complication. Diabetic foot is a direct consequence of diabetic neuropathy and vasculopathy. According to Kehkashan et al, peripheral arterial disease in diabetic patients is due to restriction of blood flow especially distal arteries of lower limb and more specifically the infrapopliteal arteries. Abnormal ankle-brachial index is found to be present in almost twenty percent diabetics, but it can be unreliable if the arteries are incompressible due to calcification. The measurement of pressures can be more reliable under such circumstances.[12] There we chose pedal acceleration time to quantify vasculopathy& neuropathy. Pedal acceleration time is a newly described modality which is thought to give valuable information regarding foot hemodynamics. Pinelo et al used it as a prognostic tool for monitoring wound healing in diabetic patients. They correlated it to transcutaneous oxygen pressure. They established that perfusion of foot was reliably gauged by pedal acceleration time. Therefore, we chose it and used it in our study. We were able to identify 20 percent of patients to have critical vasculopathy despite having fair glycemic control. These patients could have developed over limb ischemia in the early course of disease. Therefore it prudent to use non-invasive measures like PAD to screen all diabetic patients who have a decade long history of diabetes mellitus.[13] According to retrospective study by Jean-Eudes Trihan et al pedal acceleration time proved to be a promising tool for diagnosis if peripheral arterial disease as it correlated with severity of disease, and they used it to identify patients with critical limb ischemia.[14] In our study seventy-five percent of patients with severe glycemic derangements had critical vasculopathy and they did not complain about it. Moreover, we performed a prospective study and they preferred a retrospective study.

According to Stavros spiliopoulos et al, pedal acceleration accurately determined hemodynamic changes of perfusion of foot and used it to detect the foot perfusion after angioplasty of foot circulation. Thus, we relied upon the pedal acceleration time, and we found a positive correlation with severity of neuropathy.[15] we not only used pedal acceleration time but also used biochemical studies including glomerular filtration rate and serum cholesterol to correlate with severity of diabetic neuropathy. The glomerular filtration rate can also predict neuropathy as it shows a positive correlation with neuropathy.[15] Mean GFR of all patients in group under study was <90ml/min/L however it did not vary much between different severity of the neuropathy. Decline in GFR is one of clinical manifestations of diabetic neuropathy[16] but in our study it did not correlate much with severity of vasculopathy. The possible explanation is that GFR reflects significant renal damage and is not reliable to identify early stages of diabetic neuropathy.[17] The other biochemical marker we used was serum cholesterol, which correlated well with severity of diabetic neuropathy and vasculopathy. Dyslipidemia during diabetes and insulin resistance affect the function of vascular

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endothelium, promote atherosclerosis and induce oxidative stress that causes plaque formation.[18]

Diabetes peripheral neuropathy is considered a reason behind decline in driving performance. Reduced sensation of limbs can result in compromised driving.[19] Therefore, diabetic patients with long standing diabetes should be screened for peripheral neuropathy so that timely interventions can be applied.

Limitations of study: our study has few limitations. We performed a single study. We chose patients with 10 years of diabetes.

Conclusion:

We concluded doppler studies based on pedal acceleration time correlate with the severity of glycemic control. GFR did not correlate significantly with neuropathy severity, but serum cholesterol levels correlated with severity of neuropathy.

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Authors contributions:

Author 1& 2: Drafting of work 2: Design analysis 3: Data acquisition 4: Data interpretation and 5: Approval of final version to be published

Author 3& 4 : Drafting of work 2: Design analysis 3: Data acquisition 4: Data interpretation and 5: Approval of final version to be published

Author 5& 6: Drafting of work 2: Design analysis 3: Data acquisition 4: Data interpretation and 5: Approval of final version to be published

REFERENCES:

1.Oon NB, Khairudin Z, Abd Rahman HA, Kamarudin N, Abu Bakar NS, Abd Aziz NA. Prediction of diabetic retinopathy among diabetic neuropathy in T2DM patients using data mining algorithm. Malaysian Journal of Computing (MJoC). 2024;9(2):1916-29. https://doi.org/10.24191/mjoc.v9i2.26720

2.Anandhanarayanan A, Teh K, Goonoo M, Tesfaye S, Selvarajah D. Diabetic neuropathies. Endotext [Internet]. 2022 Mar 15. PMID: 25905398

3.Labeeq M, Tariq MA, Tung SA, Yar MA, Rehman W, Ehsan SB. The Economic impact of lower extremity amputations in diabetics. A retrospective study from a tertiary care hospital of Faisalabad, Pakistan. Pak J Surg Med. 2020;1(1):18-22. https://doi.org/10.5281/zenodo.3595029. https://doi.org/10.5281/zenodo.3595029.

5.Khatoon MA, Karim SM, Khan L, Karimi S, Abro UF. Exploring the Indications, Levels, and Outcomes of Lower Extremity Amputation at a Tertiary Care Hospital in Pakistan. Cureus. 2023 Nov;15(11). https://doi.org/10.7759/cureus.48856

6.Jafar TH, Haaland BA, Rahman A, Razzak JA, Bilger M, Naghavi M, Mokdad AH, Hyder AA. Non-communicable diseases and injuries in Pakistan: strategic priorities. Lancet. 2013 Jun 29;381(9885):2281-90. https://doi.org/10.1016/S0140-6736(13)60646-7.

7.Shivam, Gupta AK, Kumar S. Current Concepts in the Molecular Mechanisms and Management of Diabetic Neuropathy by Pharmacotherapeutics and Natural Compounds. Central Nervous System Agents in Medicinal ChemistryChemistry-Central Nervous System Agents). 2024 Dec 1;24(3):264-80. https://doi.org/10.2174/0118715249278438240325072758.

8.Sommerset J, Teso D, Feliciano B, et al. Innovative Arterial Duplex Examination: A Guide to Evaluate Flow in the Foot Using Pedal Acceleration Time. Journal for Vascular Ultrasound. 2019;43(1):11-17. https://doi.org/doi:10.1177/1544316719827328

9.Laxmi MS, Prabhakar O. Development of risk prediction scores for diabetic peripheral neuropathy patients. J Neurosci Rural Pract. 2023 Oct-Dec;14(4):667-670. https://doi.org/10.25259/JNRP_151_2023.

10.Hart O, Lee KT, Gormley S, August B, Abbott G, Khashram M. Association of Pedal Acceleration Time with Healing and Amputation Free Survival in Patients With

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Ulceration and Gangrene. European Journal of Vascular and Endovascular Surgery. 2024 May 31. https://doi.org/10.1016/j.ejvs.2024.05.043

11.Malik, R.A., Newrick, P.G., Sharma, A.K. et al. Microangiopathy in human diabetic neuropathy: relationship between capillary abnormalities and the severity of neuropathy. Diabetologia 32, 92–102 (1989). https://doi.org/10.1007/BF00505180

12.Parveen K, Hussain MA, Anwar S, Elagib HM, Kausar MA. Comprehensive review on diabetic foot ulcers and neuropathy: Treatment, prevention and management. World J Diabetes. 2025 Mar 15;16(3):100329. https://doi.org/ 10.4239/wjd.v16.i3.100329.

13.Pinelo A, Loureiro L, Martins J, Sommerset J, Carvalho R, Machado R. Correlation Between Pedal Acceleration Time and Transcutaneous Oxygen Pressures–A Prognostic Tool for Wound Healing in the Diabetic Foot Population. Annals of Vascular Surgery. 2024 Sep 1;106:400-7. https://doi.org/10.1016/j.avsg.2024.03.031

14.Trihan JE, Croquette M, Hersant J, Prigent R, Fontaine C, Henni S, Lanéelle D. Accuracy of maximal acceleration time of pedal arteries to diagnose critical limb-threatening ischemia. Vascular Medicine. 2024 Apr;29(2):153-62. https://doi.org/10.1177/1358863X231226216

15.Zhang YY, Chen BX, Chen Z, Wan Q. Correlation study of renal function indices with diabetic peripheral neuropathy and diabetic retinopathy in T2DM patients with normal renal function. Frontiers in Public Health. 2023 Dec 15;11:1302615. https://doi.org/10.3389/fpubh.2023.1302615

16.Kulkarni A, Thool AR, Daigavane S, Aditi S. Understanding the clinical relationship between diabetic retinopathy, nephropathy, and neuropathy: a comprehensive review. Cureus. 2024 Mar 21;16(3). https://doi.org/110.7759/cureus.56674

17.Luo Y, Zhang W, Qin G. Metabolomics in diabetic nephropathy: Unveiling novel biomarkers for diagnosis. Molecular Medicine Reports. 2024 Sep 1;30(3):1-3. https://doi.org/10.3892/mmr.2024.13280

18.Jia G, Bai H, Mather B, Hill MA, Jia G, Sowers JR. Diabetic vasculopathy: Molecular mechanisms and clinical insights. International journal of molecular sciences. 2024 Jan 9;25(2):804. https://doi.org/10.3390/ijms25020804

1.Ma S, Wu C, Zhang J, Zeng X, Zhao G, Sun X. Looking for an optimal pedal layout to improve the driving performance of patients with diabetic peripheral neuropathy. Applied ergonomics. 2019 Oct 1;80:43-9. https://doi.org/10.1016/j.apergo.2019.04.015