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Relationship between Peripheral Neuropathy and Carotid Intima-Media Thickness in Type 2 Diabetes Mellitus Patients

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Abstract

Introduction: Diabetic polyneuropathy (DPN) is the most common diabetic complication and has a lifetime prevalence of approximately 50%. Diabetic peripheral neuropathy is the leading cause of disability due to foot ulceration, amputation, and gait disturbance. Almost 20% to 30% of patients with diabetic peripheral neuropathy suffer from neuropathic pain, which significantly lowers the quality of life and dramatically increases health costs associated with diabetes. Carotid intima-media thickness (CIMT), assessed using B-mode ultrasound, has already established itself as a surrogate endpoint in monitoring subclinical atherosclerosis.

Methods: This cross-sectional study includes 200 diabetic patients who attended the diabetic clinic in Government Medical College, Kota, in 2022. CIMT was measured in the bilateral proximal internal carotid artery and mid-common carotid artery using B-mode ultrasonography. Using a vibrosense biothesiometer, the vibration perception threshold (VPT) was assessed.

Results: This study evaluated 200 diabetic patients (107 males and 93 females). Of these patients, 112 had peripheral neuropathy. Patients with peripheral neuropathy were older (65.6 ±12.9 years vs 64.1 ±13.5 years) and had a longer duration of T2DM (10.2 ± 4.8 years vs 8.3 ±4.9 years) than patients without peripheral neuropathy, p-value < 0.05. Patients with CIMT >0.8 mm had higher prevalence of peripheral neuropathy (63.4% vs 31.9% in patients with CIMT < 0.8 mm). In these patients, prevalence of hypertension was higher (82.3% vs 63.8% in patients with CIMT < 0.8 mm).

Conclusion: This study revaled a significant relationship between peripheral neuropathy and CIMT in patients of Type 2 diabetes mellitus.

Key words: Diabetes mellitus, DPN, CIMT, VPT.

Introduction

Human behaviour and lifestyle changes over the last century have resulted in a remarkable increase in the global prevalence of diabetes. The epidemic is mostly of type 2 diabetes mellitus and associbated conditions like "diabesity" and "metabolic syndrome"[1,2].

Diabetic polyneuropathy (DPN) is the most common diabetic complication and has a lifetime prevalence of approximately 50%. DPN is the leading cause of disability due to foot ulceration, amputation, and gait disturbance. Almost 20% to 30% of patients with DPN suffer from neuropathic pain, which significantly lowers the quality of life and dramatically increases health costs associated with diabetes[3]. Epidemiological studies show that type 2 diabetes has a greater prevalence of diabetic neuropathy than type 1 diabetes. Undiagnosed DPN complications lead to impaired quality of life and an increase in mortality rate. Vibration perception threshold (VPT) plays an essential role in the early detection of DPN and consequently reduces its complications.

Metabolic syndrome is a cluster of dangerous cardiovascular risk factors: central obesity, glucose intolerance, hypertension, and dyslipidaemia. People with metabolic syndrome are at higher-risk for cardiovascular disease and increased mortality. Recently, many studies have suggested that the components of the metabolic syndrome had a prominent role in the pathogenesis of peripheral neuropathy. It is generally believed that oxidative stress is the primary pathological mechanism causing nerve damage in diabetes. Oxidative stress is possibly triggered by vascular abnormalities and associated microangiopathy in the nerve. It is a crucial pathological process inducing nerve damage in diabetes in humans and experimental models[4].

DPN is a common microvascular complication with high mortality rates, but little is known about the association between DPN and atherosclerotic vascular changes. CIMT, assessed using B-mode ultrasound, has already established itself as a surrogate end-point in monitoring subclinical atherosclerosis. Recent studies have demonstrated the relationship between peripheral neuropathy and atherosclerotic vascular changes[5,6]. Furthermore, these

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studies consistently showed a relationship between functional parameters of arterial stiffness like pulse wave velocity and peripheral neuropathy. However, results regarding the relationship between CIMT and peripheral neuropathy are contradictory[5,6].

The present study explored the relationship between peripheral neuropathy and CIMT in type 2 diabetes mellitus patients.

Material and Methods

This cross-sectional study included 200 patients with established and newly diagnosed cases of type 2 diabetes mellitus of both sexes, aged between 21 to 80 years, who attended the diabetic clinic at Government Medical College, Kota, from January 2022 to April 2022. Patients with a history of alcoholism and smoking were excluded, and those with a history of ischemic heart disease and chronic kidney disease were also excluded from the study. Following an explanation of the nature and purpose of the study, subjects willing to participate were included. Ethics committee clearance and informed consent were obtained. The diagnosis of diabetes was made as per American Diabetes Association criteria. An elaborative history, including duration, co-morbidities and drug compliance, was taken, and a thorough clinical examination was performed on each participant. Anthropometric measurements of height, weight, body mass index, and waist circumference were taken. CIMT was measured in the bilateral proximal internal carotid artery and mid-common carotid artery using B-mode ultrasonography. CIMT value > 0.8 mm was considered as increased thickness[7]. Using a Vibrosense biothesiometer, the vibration perception threshold (VPT) was assessed, and a VPT value of > 25 V was taken as the standard for diagnosing peripheral neuropathy[8]. A venous blood sample was drawn and HbA1c, fasting blood sugar, fasting insulin, and lipid profile were measured.

Statistical methodology

Statistical analysis was performed using Statistical Package for Social Science (SPSS) Version 22.0. Quantitative Continuous variables data were expressed as mean ± standard deviation, whereas Quantitative discrete variables data were expressed as frequencies and numbers (%). The qualitative data were expressed in Medians with interquartile ranges. The student's t-test and χ2test were used to compare the difference for means between two or more groups or categorical variables. In contrast, continuous variables were compared using the Mann- Whitney U test. All statistical tests were two-tailed. The Pearson correlation co-efficient was computed to determine the association between 2 continuous variables. Statistical significance was taken as $p < 0.05$.

Results

This study evaluated 200 diabetic patients (107 males and 93 females). Of these patients, 112 had peripheral neuropathy. Patients with peripheral neuropathy were older (65.6 ± 12.9 years vs 64.1 ± 13.5 years) and had a longer duration of type 2 diabetes mellitus (10.2 ± 4.8 years vs 8.3 ± 4.9 years, P-value < 0.05). The prevalence of hypertension was higher in patients with peripheral neuropathy than in those without peripheral neuropathy. In addition, fasting blood sugar, fasting insulin, and triglycerides were higher in patients with peripheral neuropathy, but the results were not statistically significant (Table I and Table II).

Table I: Baseline characteristics.

Clinicopathologic Factors		Group (N=200)
Gender	Male	107 (53.5%)
	Female	93 (46.5%)
Age (years)	Mean ± SD	64.92 ± 13.12
	Range	(22 - 99)
Duration of diabetes (years)	Mean ± SD	9.4 ± 4.9
	Range	(0 - 32)
Hypertension	Yes	156 (78%)
	No	44 (22%)
Height (mt)	Mean ± SD	1.63 ± 0.08)
	Range	(1.41 - 1.84)
Weight (kg)	Mean ± SD	66.72 ± 11.65
	Range	(42 - 98)
BMI (kg/m^2)	Mean ± SD	25.09 ± 4.8
	Range	(15.9 - 39.6)
Waist Circumference (cms)	Mean ± SD	97.74 ± 7.84
	Range	(72 - 122)
FBS (mg/dl)	Mean ± SD	155.9 ± 68.6
	Range	(81 - 545)
HbA1c (%)	Mean ± SD	7.42 ± 1.53
	Range	(4 - 13.6)
Fasting Insulin (μlU/ml)	Mean ± SD	18.52 ± 16.15
	Range	(1.11 - 97.1)
TG (mg/dl)	Mean ± SD	178.98 ± 60.8
	Range	(58 - 482)
HDL (mg/dl)	Mean ± SD	44.26 ± 10.07
	Range	(28 - 81)
Cholesterol (mg/dl)	Mean ± SD	186 ± 16.28
	Range	(125 - 225)
NCV	Mean ± SD	26.76 ± 6.9
	Range	(13.95 - 52.58)
VPT	Mild	27 (13.5%)
	Moderate	61 (30.5%)
	Severe	112 (56%)
CIMT (mm)	Mean ± SD	0.86 ± 0.16
	Range	(0.40 - 2.43)
Metabolic Syndrome	Yes	155 (77.5%)
	No	45 (22.5%)

Table II: Comparative analysis of patients based on peripheral neuropathy.

Clinicopathologic Factors		Peripheral neuropathy (-) (n = 88)	Peripheral neuropathy (+) (n = 112)	F value/Chi square test (P value)	Remark
Gender	Male	53 (60.3%)	54 (48.2%)	2.859 (0.090)	Not Significant
	Female	35(39.8%)	58 (51.8%)		
Age (Years)	Mean ± SD	64.1 ± 13.5	65.6 ± 12.9	0.4361 (0.6088)	Not Significant
	Range	(22 - 92)	(33 - 99)		
Duration (Years)	Mean ± SD	8.3 ± 4.9	10.2 ± 4.8	**6.9245 (0.0091)**	**Significant**
	Range	(0 - 32)	(0 - 30)		
Hypertension	Yes	58 (65.9%)	98 (87.5%)	**13.387 (0.0002)**	**Significant**
	No	30(34.1%)	14 (12.5%)		
Height (mt)	Mean ± SD	1.63 ± 0.08	1.64 ± 0.08	0.7694 (0.3814)	Not Significant
	Range	(1.45 - 1.84)	(1.41 - 1.84)		
Weight (kg)	Mean ± SD	67.5 ± 13.1	66.1 ± 10.4	0.7028 (0.4028)	Not Significant
	Range	(42 - 98)	(45 - 96)		
BMI (Kg/m^2)	Mean ± SD	25.51 ± 5.2	24.78 ± 4.5	1.149 (0.284)	Not Significant
	Range	(16.7 - 39.6)	(15.9 - 36.8)		
Waist Circumference (cms)	Mean ± SD	97.8 ± 7.9	97.7 ± .7.8	0.03199 (0.8582)	Not Significant
	Range	(78 - 122)	(72 - 115)		
FBS (mg/dl)	Mean ± SD	150.8 ± 55.5	159.9 ± 77.3	0.8669 (0.3529)	Not Significant
	Range	(85 - 362)	(81 - 345)		
HbA1c (%)	Mean ± SD	7.34 ± 1.48	7.49 ± 1.58	0.4780 (0.4901)	Not Significant
	Range	(4 - 11.6)	(4.8 - 13.6)		
Fasting Insulin (μIU/ml)	Mean ± SD	17.15 ± 14.2	19.59 ± 17.52	1.1303 (0.2889)	Not Significant
	Range	(1.28 - 69.6)	(2.30 - 97.1)		
TG (mg/dl)	Mean ± SD	173.4 ± 49.9	183.3 ± 68.1	1.3049 (0.2546)	Not Significant
	Range	(91 - 412)	(58 - 482)		
HDL (mg/dl)	Mean ± SD	43.5 ± 9.8	44.9 ± 10.3	0.9055 (0.3424)	Not Significant
	Range	(30 - 81)	(28 - 72)		
Cholesterol (mg/dl)	Mean ± SD	185.4 ± 18.9	186.4 ± 13.9	0.2142 (0.6439)	Not Significant
	Range	(125 - 225)	(154 - 225)		
VPT (v)	Mean ± SD	21.6 ± 2.80	30.85 ± 6.38	**162.06 (0.000)**	**Significant**
	Range	(13.95 - 24.96)	(25.07 - 52.58)		
CIMT (mm)	Mean ± SD	0.82 ± 0.12	0.90 ± 0.17	**12.78 (0.0004)**	**Significant**
	Range	(0.40 - 1.18)	(0.6 - 2.43)		
Metabolic Syndrome	Yes	64 (72.7%)	91 (81.3%)	2.053 (0.151)	Not Significant
	No	24 (27.3%)	21 (18.8%)		

Table II shows that the CIMT value was higher among peripheral neuropathy subjects (0.90 ± 0.17 mm vs 0.82 ± 0.12 mm) than among patients without neuropathy, (p-value < 0.05). In our study, out of 200 patients, 155 patients had metabolic syndrome. The peripheral neuropathy group had more patients with metabolic syndrome (81.3% of patients with peripheral neuropathy had metabolic syndrome vs 72.7% of patients without peripheral neuropathy had metabolic syndrome, but the results were not significant).

Table III shows that patients with CIMT > 0.8 mm had a higher prevalence of peripheral neuropathy (63.4% vs 31.9% in patients with CIMT < 0.8 mm). In these patients prevalence of hypertension was higher (82.3% vs 63.8% in patients with CIMT < 0.8 mm). Patients with CIMT > 0.8 mm had a longer duration of diabetes (10.9 ± 4.13 years vs 4.96 ± 4.36 years), and more patients had metabolic syndrome (81.6% vs 66.7%); all these results were statistically significant.

Table III:

Clinicopathologic Factors		CIMT< 0.8 mm (n = 47)	CIMT ≥ 0.8 mm (n = 153)	Chi square test	(p value)	Remark
Peripheral neuropathy (VPT)	Negative	32 (68.1%)	56 (4.6%)	14.464	**0.0001**	**Significant**
	Positive	15(31.9%)	97 (63.4%)			
Hypertension	Yes	30(63.8%)	126 (82.3%)	7.1891	**0.0073**	**Significant**
	No	17(26.2%)	27 (17.7%)			
Metabolic Syndrome	Yes	31 (66.7%)	124 (81.6%)	4.6941	**0.0302**	**Significant**
	No	16 (33.3%)	29 (19.4%)			
Duration of diabetes (years)	Mean ± SD	4.96 ±4.36	10.9 ± 4.13	77.316	**<0.0001**	**Significant**
	Range	(0-17)	(4 - 32)			

Table IV shows that VPT positively correlated with duration of diabetes (r value = 0.242), fasting blood sugar (r value = 0.194), fasting insulin (r value = 0.146) and CIMT (r value = 0.244).

Table IV: Pearson correlation of different variables with VPT.

Parameters	R value (Pearson correlation co-efficient)	P value	Results
Age (in yrs)	-0.048	0.501	Not significant
Duration of diabetes	0.242	**0.001**	**Significant**
Height	0.047	0.504	Not significant
Weight	-0.50	0.484	Not significant
BMI	-0.66	0.353	Not significant
Waist Circumference	-0.20	0.777	Not significant
FBS	0.194	**0.006**	**Significant**
HbA1c	0.117	0.099	Not significant
Fasting Insulin	0.146	**0.039**	**Significant**
Triglycerides	0.051	0.471	Not significant
HDL	0.054	0.447	Not significant
Total Cholestrol	0.086	0.225	Not significant
CIMT	0.244	**0.001**	**Significant**

Discussion

Cardiovascular disease is a major complication of type 2 diabetes, and atherosclerosis is usually asymptomatic in these patients. Atherosclerosis is a multifactorial disease, frequently involving the entire arterial system. Thus, the severity of atherosclerotic change in any segment of the arterial system can provide information about involvement in other arterial systems. Therefore, determining the extent of atherosclerosis in carotid arteries, that are easily visualised, may provide information about the presence and severity of coronary atherosclerosis.

Increased CIMT, an early marker of atherosclerosis, was significantly higher in the peripheral neuropathy group than in the group without peripheral neuropathy. Many previous studies found a relationship between peripheral neuropathy and functional parameters of arterial stiffness like brachial-ankle pulse-wave velocity (PWV) and brachial pulse pressure (PP)[9]. In the present study, we also demonstrated a positive correlation between CIMT (an early atherosclerosis marker) and VPT. Patients with CIMT > 0.8 mm had more peripheral neuropathy than those with CIMT < 0.8 mm. A previous study demonstrated that CIMT was higher in patients with versus without peripheral neuropathy, which is one of the chronic complications of diabetes[5]. It has been found that intima-media thickening, an early sign of atherosclerosis, is associated with cardiovascular risk factors. Many studies suggest that increased CIMT is associated with an increased risk of stroke and silent cerebral infarction[10]. Patients with peripheral neuropathy were older and had a longer duration of diabetes. In addition, patients with severe peripheral neuropathy had a higher prevalence of hypertension. Forrest *et al*, found that hypertensive individuals had a significantly increased risk of developing DPN in a 6-year follow-up study[11]. There was also a significant positive correlation between peripheral neuropathy and fasting blood glucose and insulin. Dyck *et al* found a strong correlation between hyperglycaemia and peripheral neuropathy[12]. Many studies demonstrated a relationship between age and duration of diabetes with peripheral neuropathy, similar to our study[13,14].

Metabolic syndrome is also associated with increased CIMT. In the present study, CIMT values were higher (> 0.8 mm) among the patients of metabolic syndrome compared to patients without metabolic syndrome, and the results were statistically significant. Similar findings were observed in other studies in which metabolic syndrome was associated with increased CIMT progression[15,16].

It is generally believed that oxidative stress is the primary pathological process inducing nerve damage in diabetes. Oxidative stress, possibly triggered by vascular abnormalities and associated microangiopathy in the

nerve, is a crucial pathological process causing nerve damage in diabetes in humans and experimental models. Other possible mechanisms include decreased Na+/K+ ATPase activity, increased vasoconstrictors such as thromboxane A2 and endothelin levels, and decreased vasodilators such as prostaglandin I2 and nitric oxide, increased aldose reductase activity, and fatty deposition in nerves, extracellular protein glycation, mitochondrial dysfunction[2,4].

Limitations: It was a cross-sectional design, thus it was not possible to establish a cause-and-effect relationship between peripheral neuropathy and CIMT. Further, small sample size of the study population also limits the generalisation of the results.

Conclusion

This study determined a significant relationship between peripheral neuropathy and CIMT in patients with type 2 diaetes mellitus. Early detection of peripheral neuropathy might help prevent macrovascular complications of diabetes. Furthermore, evolving data suggest that exercise and weight reduction strategies are helpful in patients with peripheral neuropathy in the setting of diabetes and metabolic syndrome, along with glycaemic control. Thus, implementing strategies that target these modifiable risk factors can help prevent and control the chronic complications of type 2 diabetes mellitus.

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