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Diabetic Peripheral Neuropathy as a Predictor of Asymptomatic Myocardial Ischaemia in Prediabetics and/or Asymptomatic Type 2 Diabetes Mellitus Cases

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Abstract

Background: Diabetic peripheral neuropathy is a common and frequent complication of diabetes mellitus/prediabetes. Studies propose that a strong association exists between myocardial ischaemia due to coronary microvascular dysfunction and neuropathies in diabetes mellitus presenting with myocardial ischaemia and high mortality.

Aim: To know the relationship of diabetic peripheral neuropathy as a predictor of asymptomatic myocardial ischaemia with prediabetes and/or asymptomatic type 2 diabetes mellitus.

Methods: 60 age and gender matched cases of prediabetes and/or asymptomatic type II diabetes (30 each) were recruited in the study. The nerve conduction in the tibial motor and sural sensory nerves were measured and electrophysiological changes expressed in terms of changes in latencies, amplitude, and velocity. SPECT scans with technetium 99m were carried-out for assessing micro ischaemia in asymptomatic diabetes and /or prediabetes with/without Diabetic peripheral neuropathy (DPN). Myocardial ischaemia was expressed as summed stress score (SSS) of > 4 or two regional involvement despite normal stress score.

Results: The findings revealed that patients in prediabetes and asymptomatic diabetes group having evidence of peripheral neuropathy had positive summed stress score value significantly higher than cases without diabetic neuropathy. These positive patients were free of other cardiovascular events independently from other risk factors, viz., lipid profile, BMI, gender, HbA1c.

Conclusion: Diabetic peripheral neuropathy can exist before the onset of overt diabetes mellitus type II. Subjects of prediabetes/ asymptomatic diabetes have shown strong linkage with asymptomatic myocardial ischaemia proven on SSS score on SPECT study. We strongly feel it is not the presence of diabetes mellitus per se but cases of diabetes mellitus/prediabetes/asymptomatic diabetes with peripheral neuropathy should be considered as a strong predictor of asymptomatic myocardial ischaemia.

Keywords: DPN - Diabetic peripheral neuropathy, SPECT - Single photon emission computed tomography, SSS - Summed stress score, BMI - Body mass index.

Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common complications of prediabetes and diabetes, has been associated with ischaemic cardiovascular disease, and is the leading cause of mortality in diabetics and prediabetics. Pre-diabetes is one of the most important aetiological factor of asymptomatic myocardial ischaemia due to coronary micro vascular dysfunction. Studies propose that an association exists between cardiovascular autonomic neuropathy presenting with asymptomatic myocardial ischemia with high mortality.The relationship of DPN of asymptomatic type 2 diabetes and/or prediabetes with myocardial ischaemia has been established meagerly in literature. Hence, early recognition of patients with pre-diabetes or asymptomatic type 2 diabetes who are at high risk of developing asymptomatic myocardial ischaemia remains a significant challenge[1].

2 - 4% of normal healthy individuals may have asymptomatic myocardial ischaemia[2]. Asymptomatic myocardial ischaemia may be the reason for their inability to reach pain threshold, lesser severity of pain, shorter duration which may go unnoticed by the patients due to higher beta endorphin levels and inflammatory cytokines[3].

The present study is aimed to assess the association between DPN and asymptomatic myocardial ischaemia (Micro-ischaemia). For confirming myocardial ischaemia, SPECT Scans were carried-out with the help of technetium 99. To the best of our knowledge this kind of study for assessing micro ischaemia in asymptomatic diabetics and/ or prediabetics with/without DPN is not available in the Indian literature. A humble attempt is made in this direction in the present study.

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Material and methods:

Study Design: Cross-sectional

Study duration: 24 months. Study was conducted at MGM Hospital, Aurangabad.

Sample size: A total sample size of 60 patients diagnosed with prediabetes and/or asymptomatic diabetes in the hospital was included in the study population.

The study population for the present study was divided into two groups:

- Group 1 - Pre-diabetics/asymptomatic type 2 diabetics with peripheral neuropathy (n = 30)
- Group 2 - Pre-diabetics/asymptomatic type 2 diabetics without peripheral neuropathy (n = 30)
- All the subjects of the study were enrolled and assigned to one of the above two groups after verifying their compliance with inclusion and exclusion criteria.

Inclusion criteria: Adult patients more than 18 years of both genders with pre-diabetes status and/or asymptomatic diabetes, according to ADA and IDF criteria[4].

Table A: Diagnostic criteria for diabetes and pre-diabetes. (ADA 2016).

Diagnosis	Fasting plasma glucose	2-hour OGTT	HbA1c
Normal	< 100 mg/dl (5.6 mmol/l)	< 140 mg/dl (7.8 mmol/l)	< 5.7%
Pre-diabetic	100 - 125 mg/dl (5.6 - 6.9 mmol/l)	140 - 199 mg/dl (7.8 - 11 mmol/l)	5.7 - 6.4%
Diabetic	≥ 126 mg/dl (7.0 mmol/l)	≥ 126 mg/dl (11.1 mmol/l)	≥ 6.5%

Exclusion criteria

- Those patients who were NOT willing to participate in the study.
- Any history of myocardial infraction, stroke, coronary revascularisation.
- Patients with any active liver disease or autoimmune disease or malignancy or HIV infection.
- Patients with past history of spinal injury, carpel tunnel syndrome and any other neuropathy.
- Patients having concomitant use of drugs like isoniazid, glucocorticoids and metronidazole.

Methodology

- 60 patients with diagnosis of pre-diabetes and/or asymptomatic type 2 diabetes were recruited for the study.
- As per the nerve conduction studies (NCS) they were sub grouped into group I – with neuropathy and group II - without neuropathy.
- All cases were subjected to Technetium-99m assessment for ischaemic heart disease.
- NCS were carried-out under the care of neuro physician for all cases and data was recorded for evaluation.
- SPECT scans with Technetium-99m were carried-out under the care of Nuclear Medicine Physician for all cases and data was recorded for evaluation.

Outcome measurements

- All patients who had undergone Technetium-99m Sestamibi single-photon Emission computed tomography imaging were assessed for the estimation of myocardial ischaemia, expressed as Summed stress score (SSS); or two regional affections despite normal stress score[5].
- Neuropathy was assessed with clinical scores as well nerve conduction studies to quantify DPN abnormality.
- RR ratio on ECG was also calculated and a ratio less than 1.04 was taken to indicate cardiac autonomic neuropathy.

Statistical analysis

- All participants underwent haematological investigations, Nerve conduction study and SPECT scan. The data was compiled and analysed using SPSS version 22. All parameters were expressed in means +/- SD. For comparison of DPN positive and DPN negative group's unpaired t-test was used. The chi-square test was used to check significance of association between different groups and outcome of different variables. P value was checked at 5% level of the significance.

Results

In the present study, we compared variables between groups of DPN positive and DPN negative subjects for evidence of myocardial ischaemia, detected on SPECT scan. Table I shows distribution of patients, according to age, in DPN positive and DPN negative groups with no statistically significant difference.

Table II shows a comparison of mean BMI and HbA1c in both groups. The mean BMI was more in group I as compared to group II with no statistically significant difference. Similarly, parameters like mean blood sugar level, HbA1c estimations revealed no statistically significant difference

in the groups. Table III shows comparison of mean lipid profile of patients in the studied groups. The values observed were statistically not different.

Table I: Age-group of patients in groups.

Age-group	Group I (DPN positive)		Group II (without DPN)	
	No of cases	Percentage (%)	No of cases	Percentage (%)
≤ 30 years	02	6.67	03	10.0
31 - 40	05	16.67	02	6.67
41 - 50	07	23.33	06	20.0
51 - 60	09	30.0	12	40.0
61 - 70	04	13.33	06	20.0
> 70	03	10.0	01	3.33
Total	30	100	30	100
Mean ± SD	51.47 ± 14.68		52.40 ± 13.14	
t - value	0.259			
P - value	0.796 NS			

(DPN - Diabetic peripheral neuropathy).

Table II: Comparison of mean BMI of patients in groups.

	Group I (DPN positive) Mean ± SD	Group II (without DPN) Mean ± SD	t - value	P - value
BMI (kg/m^2)	26.60 ± 3.76	25.67± 2.79	1.09	P = 0.279 NS
HbA1C (%)	7.47 ± 2.39	7.33± 1.92	0.255	P = 0.792 NS

DPN - Diabetic peripheral neuropathy, BMI - Body mass index, NS -Not significant.

Table III: Comparison of mean lipid profiles of patients in groups.

	Group I (DPN positive) Mean ± SD	Group II (without DPN) Mean ± SD	t - value	P - value
S. cholesterol (mg/dl)	167.30 ± 33.26	173.26 ± 39.05	0.637	P = 0.528 NS
TG (mg/dl)	145.60 ± 40.68	154.70 ± 86.47	0.522	P = 0.604 NS
LDL (mg/dl)	87.21 ± 18.96	89.43 ± 21.37	0.426	P = 0.672 NS
HDL (mg/dl)	40.10 ± 12.29	37.50 ± 11.94	0.831	P = 0.409 NS

DPN - Diabetic peripheral neuropathy, TG - Triglycerides, LDL - Low density lipoproteins, HDL - High density lipoproteins, SD - Standard deviation, NS - Not significant.

Table IV shows a comparison of patients in both groups according to RR ratio. The RR ratio was more in group I as compared to group II. However, the observations were statistically not different.

Table IV: RR ratio of patients in groups.

RR Ratio	Group I (DPN positive)		Group II (without DPN)		Chi-square value	P - value
	No of cases	Percentage (%)	No of cases	Percentage (%)		
Normal	25	83.33	29	96.67	2.96	P = 0.085
Abnormal	05	16.67	01	03.33		NS
Total	30	100	30	100		

DPN: Diabetic peripheral neuropathy, RR: RR ratio on ECG, NS: Not significant

Table V shows association between SSS (summed stress score) and DPN groups. It was observed that SSS in group I (DPN positive cases) was abnormal in 5 (16.7%) patients as compared to nil patients in group II (DPN negative). There was a statistical difference among both groups with respect to SSS ($P < 0.05$).

Table V: Association between SSS and DPN groups.

Summed stress score (SSS)	Group I (DPN positive)		Group II (without DPN)		Chi-square value	p-value
	No of cases	Percentage (%)	No of cases	Percentage (%)		
Normal (< 4)	25	83.3	30	100.0	5.45	P = 0.020 S
Abnormal (> 4)	05	16.7	00	00		
Total	30	100	30	100		

(DPN: Diabetic peripheral neuropathy, S: Significant.

Table VI shows association of SSS with smoking and dyslipidemia in group I. It was observed that SSS among smokers was abnormal in 5 (80 %) patients as compare to non-smokers (20 %) the difference observed is significant statistically but it is insignificant for dyslipidaemias and HbA1c.

Table VI: Abnormal SSS of group I patients with smoking and lipid profile.

		Abnormal SSS (n = 05)	Normal SSS (n = 25)	Chi-square value	P-value
Smoking	Smoker	04 (80.0%)	09 (36.0%)	3.79	P = 0.034 S
	Non-Smoker	01(20.0%)	16 (64.0%)		
Lipid profile	Abnormal	01 (20.0%)	09 (36.0%)	0.480	P = 0.488 NS
	Normal	04(80.0%)	16(64.0%)		

S: Significant, NS: Not significant, SSS-Summed stress score.

Table VII shows comparison of mean Michigan scoring in both groups. It was observed that Michigan scoring and clinical Michigan scoring in group I and group II was significant in either groups.

Table VII: Comparison of mean Michigan scoring of patients in groups.

Michigan scoring	Group I (DPN positive) mean ± SD	Group II (without DPN) mean ± SD	t - value	P - value
History	4.03 ± 1.24	2.00 ± 0.74	7.68	P < 0.0001 S
Clinical	2.40 ± 1.04	0.73 ± 0.98	6.39	P < 0.0001 S

DPN: Diabetic peripheral neuropathy, S: Significant.

Discussion

The present study was undertaken for assessing presence of diabetic peripheral neuropathy as a predictor of asymptomatic myocardial ischaemia in pre-diabetes and/or asymptomatic type 2 diabetes mellitus subjects.

Myocardial ischaemia (MI) was diagnosed using electrocardiographically gated technetium-99m SPECT tomographic images.The summed stress score (SSS) which shows the degree and seriousness of perfusion variation from the normal was considered unusual when scores were more than or equal to 4 (≥ 4).The value of 4 as significant has been considered by many other workers[6,7]. Also when involvement of two different anatomical regions of myocardial ischaemia was seen on SPECT even though values of SSS score remains less than 4 was taken as a positive value for evidence of myocardial ischaemia (MI)[5].

Diabetic peripheral neuropathy (DPN) was evaluated for neuropathy using Michigan criteria by history and testing sensation of pain, touch, cold and vibrations in either legs and assigning a score according to the level of impaired sensation. Additionally, all groups were examined for sensation with monofilament tests.

The neuropathic diagnosis was ascertained besides history, clinical examination by undertaking nerve conduction studies in all cases. Electro diagnostic findings used for localising limb neuropathies were recordings of focal slowing, changes in SNAPs/CMAPs, NCV changes in all cases. Autonomic neuropathies were suspected on basis of features of orthostatic hypotension, RR Ratio calculation. The anomalous RR proportion was considered as autonomic dysfunction when RR proportion was under 1.04.

Diabetic peripheral neuropathy is one of the most common complications of diabetes mellitus and has been associated with cardiovascular disease like asymptomatic myocardial ischaemia. The present work is based on the hypothesis that presence of peripheral neuropathy may be associated with myocardial ischaemia in patients with diabetes mellitus, pre-diabetes and asymptomatic diabetes. We understand and believe that diabetes mellitus is a pivotal cause of asymptomatic myocardial ischaemia even in the absence of coronary artery disease. Early diagnosis of diabetes has great value and this group includes pre-diabetes and asymptomatic status also.

DPN has very good predictive value for asymptomatic myocardial ischaemia as we found by SPECT imaging in group I pre-diabetic/asymptomatic diabetic patients. 05 of 30 patients in group I were positive for Summed stress score (SSS) as against none in non DPN group II cases.The difference observed was statistically significant among both groups with respect to SSS (P < 0.05).These positive patients were free of cardiovascular events independently from other risk factors, viz., lipid profile, BMI, gender, HbA1C. However, smoking history was significantly noted in DPN positive group.The present observational analysis suggests that association between DPN (in pre-diabetics and asymptomatic diabetic) and myocardial ischaemia could suggest a role of neuropathy as a possible predictor of cardiovascular morbidity. DPN, is traditionally counted among microvascular complication caused by neuronal cell abnormalities, oxidative and/or inflammatory injury in nature affecting the endothelium.

Dimitrios Baltzis *et al* did a study in 2016[3] in which he studied diabetic patients to evaluate the predictability of peripheral neuropathy in asymptomatic myocardial ischaemia and showed abnormal SSS was more in DPN group as compared to non DPN with statistical difference. Similar findings were revealed by Zellweger *et al*[8].

Brownrigg *et al* in 2005[6] also established the relationship between DPN and cardiovascular risk factors.The association between diabetic neuropathy and MI exceeds autonomic neuropathy. Diabetic peripheral neuropathy currently is related with the expanded frequency of CVD, despite of the fact that interrelationship of these two conditions has not been clearly defined in the literature.

Conclusion

Cases of pre-diabetes and/or asymptomatic diabetes were studied under 2 groups as cases with peripheral neuropathy group I (30 cases) and cases without neuropathy group II (30 cases). Cases were analysed for the presence of diabetic peripheral neuropathy using Michigan criteria and nerve conduction studies and myocardial ischaemia was studied with SPECT scan.

Diabetic peripheral neuropathy can exist before the onset of overt diabetes mellitus. In the present study subjects of prediabetes were shown to have strong linkage with asymptomatic myocardial ischaemia as proven on SSS score on SPECT. In group I pre-diabetes/ asymptomatic diabetic patients 05 of 30 were positive for summed stress score as against none in non-DPN group II cases.The difference was

observed statistically significant with respect to SSS and these positive patients were free from other cardiovascular events independently from other factors, viz., lipid profile, BMI, HbA1c, gender; however, smoking history was significantly noted in DPN positive group. The clinical diagnosis of DPN is observer dependent and often has subjectivity errors; hence need for nerve conduction study. For ischaemia assessment only one experienced physician had undertaken SPECT imaging analysis. We strongly feel that it's not the presence of the diabetes mellitus alone but diabetes mellitus/pre-diabetes associated with peripheral neuropathy that must be considered as a strong predictor of asymptomatic myocardial ischaemia.

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