ORIGINAL RESEARCH PAPER

General Medicine

"STUDY TO DETERMINE THE PREVALENCE OF PERIPHERAL NEUROPATHY IN ADULTS WITH PRE-DIABETES IN SOUTH INDIAN POPULATION"

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ABSTRACT

Background: Peripheral neuropathy in pre diabetics has been studied in the past with supportive and negative reports with less date in the rural population. Aim was to study the frequency of peripheral neuropathy in pre diabetics in a tertiary health care centre serving the rural population.

Methods: 45 patients of prediabetes were enrolled for this study; preformed proforma was used to collect the information, data on examination and investigations. Patients with age >18 and less than 55 were selected for the study. All subjects with evidence of prediabetes were included with both gender subjects with B12 deficiency, chronic alcoholic were excluded from the study. Then these patients were subjected to nerve conduction studies.

Results: Out of total 45 pre diabetic patients 7(15.5%) were diagnosed having peripheral neuropathy. Maximum number of pre diabetic patients were (25)55.5% in the age group 46-55 years with mean age of 44.49 years ±7.01 (S.D.). 25 (55.55%) were males with a female to male ratio of 1:1.25. Out of total 7(15.5%) patients having evidence of Peripheral Neuropathy 5 were meeting all three criteria for Prediabetes while 6 had IFG, 5 patients had IGT. 42% of the patients were fulfilling the criteria of metabolic syndrome. 24 had raised TGs and out of them 4 had peripheral neuropathy. Out of 26 obese patients, 4 had peripheral neuropathy. Out of 7 patients with peripheral neuropathy 5 patients were considered to be suffering with peripheral neuropathy on the basis of sensory symptoms and 4 were considered on the basis of impaired vibration and position sense on examination, one patient diagnosed on the basis of nerve conduction studies. Mean compound motor action potential (CMAP) and nerve conduction velocity (NCV) were less in patients with peripheral neuropathy in comparison to patients without peripheral neuropathy.

Conclusions: Peripheral neuropathy can occur in prediabetes and with clinical manifestations and evident by examination. Most common is small fiber neuropathy. But by diagnosing it early in the course of prediabetes, morbidity and mortality secondary to neuropathy can be prevented.

INTRODUCTION:

As we in the current scenario of developing nature and modernalization of the world T2DM is playing a major role in the economic burden, high morbidity and mortality due to its micro and macro vascular complications. It's more important factor that T2DM just displays the tip of iceberg and the hidden pre diabetic is the challenging issue to identify and manage. It was estimated that there were about 77.2 million people with Prediabetes in India as of 2011. (1) Prediabetes is a high-risk state for DM with annualized conversion rate of 5-10% and similar percentage converting back to normal.

There is an enormous global burden of pre-diabetes, currently estimated to affect 374 million people worldwide and projected to increase to 548 million (8.6% of the global adult population) by 2045.(2) Pre-diabetes is associated with an increased incidence of diabetes-specific microvascular and macrovascular complications,(3) and an increase in cardiovascular events and all-cause mortality,(4) compared with age-matched and body mass index (BMI)-matched people with normal glucose tolerance (NGT). Indeed, the excess risks of a major event (defined as fatal/ non-fatal cardiovascular disease or all-cause mortality) were 17% and 12% based on WHO and American Diabetes Association (ADA) criteria, respectively. (4)

End-organ complications of hyperglycemia may therefore be apparent prior to the diagnosis of type 2 diabetes. (5) Unfortunately, people with pre-diabetes and concomitant microvascular disease are also more likely to develop type 2 diabetes. (6) Furthermore, the prevalence of diabetic peripheral neuropathy (DPN) has been reported as high as 35% (95% CI: 15% to 55%) at the time of diagnosis of type 2 diabetes, suggestive of an early subclinical disease phase.(7)

Although several studies have reported peripheral neuropathy in pre-diabetes, data in this area is conflicting, with some studies showing a high prevalence of peripheral neuropathy and others suggesting a low prevalence. Hence we planned to study the frequency of peripheral neuropathy in pre diabetics in a tertiary health care centre.

METHODS

The study was conducted in sri venkateshwaraa medical college hospital and research centre – Pondicherry, which is a rural serving tertiary care centre. Study was conducted from July 2019 to January 2020 for a period of six months in patients attending to the Medical OPD and admitted to Medical wards. Institutional Ethical committee clearance was taken. The patients who were of age >18 years and <55 years and were screened if they were having risk factors like family history of T2DM, obesity, dyslipidemia, history of sedentary life style, waist circumference >80cm in females and >90cm in males. Study populations of 45 patients fulfilling criteria for prediabetes were selected. Detailed history was taken and detailed examination was done. All relevant investigations were done and these patients were subjected to nerve conduction studies. All the data was recorded on preformed proforma. All patients of both genders fulfilling the criteria of Pre diabetes were included in the study willing to participate. Patient with history of chronic alcoholic, B12 deficiency, malignancy, on steroid therapy and chronic demylinating disease were excluded.

Diagnosis: Prediabetes is diagnosed when one of following criteria is fulfilled. (8)
1. Impaired fasting glucose (IFG) = 100-125 mg%
2. Impaired glucose tolerance (IGT) = 140-19mg% serum glucose at 2 hours following oral glucose challenge with 75gm of glucose.
3. HbA1C = 5.7-6.4%.

The ADA recommends screening of all individuals > 45 years age every 3 years and at a younger age if they are overweight (BMI 25kg/m2) or have additional risk factors. (9)

Clinical diagnosis of DSPN: It is based on symptoms and signs of neuropathy in a patient of Prediabetes or Diabetes in whom other causes of neuropathy have been excluded. History and physical examination will lead to clinical diagnosis of Peripheral Neuropathy in Prediabetes. In physical examination resting tachycardia, postural hypotension, and decreased variability of heart rate in response to respiration or exercise give clue for autonomic neuropathy. On examination loss of deep tendon reflexes, involvement of 3rd, 4th, 6th and 7th cranial nerves, impaired or loss of pin prick and temperature sensation, and loss of vibration and position sense can be seen.

Electro diagnostic studies: Electro diagnostic evaluation of patients of suspected neuropathy includes nerve conduction studies (NCS) and needle electromyography (EMG). Electro diagnostic evaluation can ascertain whether the process involves only sensory fibers, motor fibers, autonomic fibers, or a combination of these. And finally electro physiologic studies can differentiate myelinopathies from axonopathies. (10) It can be difficult to document a small fiber neuropathy because the only abnormalities on neurologic examination may be loss of pin prick and temperature sensation in a distal distribution whereas EMG/NCS may be normal. As a result small fiber neuropathy remains primarily a clinical diagnosis. (11)

Statistical analysis
Data was recorded on a Microsoft Excel spreadsheet. All discrete variables were expressed as percentages. Statistical analysis was performed and SPS student version 22.0. All discrete variables were expressed as percentages.

RESULTS
Table 1: Distribution of peripheral neuropathy in prediabetic patients

Prediabetic patients	n=45	%
Total number of patients diagnosed with peripheral neuropathy	7	15.5
Total number of patients without neuropathy	38	84.5

Table 2: Age group distribution of prediabetes and peripheral neuropathy

Age groups (years)	Prediabetic		Peripheral neuropathy	
	n=45	%	n=7	%
18-25	0	0	0	0
26-35	05	11	1	14.2
36-45	15	33.3	2	28.5
46-55	25	55.5	4	57.14

Table 3: Distribution of prediabetes and peripheral neuropathy according to sex

Distribution of sex	Prediabetics		Peripheral neuropathy	
	n=45	%	n=7	%
Male	25	55.5	4	57.14
Female	20	44.4	3	42.8

Table 4: Distribution of prediabetes and peripheral neuropathy in rural and urban areas

Distribution	Prediabetes patients		Peripheral neuropathy	
	n=45	%	n=7	%
Rural	39	86.6	5	71.4
Urban	06	13.3	2	28.57

Table 5: Distribution of physical activity among all pre diabetics.

Physical activity	Pre diabetics		Urban dwelling	
	n = 45	%	n=7	%
Exercise or strenuous work	23	51.1	1	16.6
Moderate physical activity at work/home	15	33.3	3	50
Sedentary work and no exercise	7	15.5	3	33.3

Table 6: Characteristics of pre diabetics.

Symptoms	Prediabetes	
	n =45	%
Paresthesia	05	11.1
Weakness	00	00
Polyuria	08	17.7
Polydypsia	05	11.1
Polyphagia	00	00
HTN	10	22.2
CVD	2	4.4
Family history of T2DM	10	22.2
Smoker	09	20
Waist circumference>90 cm in males and >80 cm in females	40	88.8
Fasting TG >150mg/dl	24	53.3
Metabolic syndrome	36	80
Vibration and position impaired	4	8.8
Touch, pain or temperature impaired	0	0
BMI 23-27.5	10	22.2
BMI>27.5	26	57.7

Table 7: Distribution of glycemic status of all patients

Glycemic status	Prediabetics		Peripheral neuropathy	
	n=45	%	Present	%
Impaired FBG	40	88.8	6	16.1
IGT	38	84.4	5	17.0
HbAIC (5.7-6.4%)	42	93.3	6	16.1
IFG+IGT	36	80	3	15.0
IFG+HbA1C (5.7- 6.4%)	42	93.3	7	17.0
IGT+HbA1C (5.7- 6.4%)	35	77.7	5	17.9
IFG+IGT+HbA1C (5.7-6.4%)	32	71.1	4	15.7

Table 8: Comparison of CMAP and NCV in the patients of peripheral neuropathy vs patients without peripheral neuropathy

NCS	Mean average in all patients	Mean average in patients with peripheral neuropathy	Mean average in patients without peripheral neuropathy
CMAP (m V)	11	5.5	12.39
NCV(m/s)	46.5	45	46.9

DISCUSSION
It has been found in various observational studies done till now that many micro and macro vascular complications start developing earlier to the diagnosis of T2DM. So it becomes very important to diagnose this earlier stage of T2 DM i.e. Prediabetes. It is at this stage when one can prevent progression of Pre diabetes to frank T2DM.Insulin resistance; metabolic syndrome and Prediabetes are closely related to each other and have overlapping aspects. Nearly 20 % of newly diagnosed T2DM patients have features of DSPN at the time of diagnosis of Diabetes.This suggests that many of them might have developed peripheral neuropathy during pre diabetic state.

Peripheral nerves include cranial nerves, spinal nerve roots, the dorsal root ganglia, peripheral nerve trunks, their terminal branches, and the peripheral autonomic nervous system. Pathogenesis of diabetic neuropathy involves an interaction of metabolic and ischemic factors. (12) Clinical presentation of peripheral neuropathy in Diabetes and Prediabetes is variable. Distal sensorimotor polyneuropathy (DSPN) presenting with symptom of pain is one of the commonest presentation. (13) Typical peripheral neuropathy is distal symmetrical sensorimotor polyneuropathy in Diabetes or Prediabetes. Any variation in presentation is atypical. Distal portion of long nerve fibers are affected in glove and stocking pattern initially. (13)

This prospective observational study included a total number

of 45 patients of prediabetes, who presented to the department of medicine, diabetology and department of neurology in this institute. Those who were fulfilling the criteria for this study were subjected to nerve conduction studies. Out of total 45 patients 7 (15.5%) were found to be suffering from peripheral neuropathy. Most previous studies reported increased prevalence of peripheral neuropathy in prediabetes, though few studies raised doubts on this association. Dan Ziegler and his team reported a prevalence of polyneuropathy to be 28% in diabetic subjects, 13% in those with IGT, 11.3% in those with IFG, and 7.4% in NGT.(14) Franklin GM et al, in another study reported prevalence of peripheral neuropathy in control, IGT, and T2DM as 3.9%, 11.2% and 25.8% respectively.(15) In this study, we had no controls and T2DM patients for comparison, but frequency of peripheral neuropathy was 15.5%, though methods of diagnosing peripheral neuropathy were different in this study. Maximum patients were in the age group of 46-55 years, as expected as incidence of diabetes increases with age. In this study 11.1% patients had paresthesia, 17.7% had polyuria and 11.1% had polydipsia. We could not find such data for comparison in literature. In this study out of 45 patients 23 (51.1%) were doing exercise or strenuous activity, 15 (33.3%) were doing moderate activity and 7 (15.5%) were doing sedentary activity, as per history on the basis of Indian diabetes risk score.

Gregory A Nicholas et al, described association of impaired fasting blood glucose, higher BMI, HTN, raised triglycerides and low HDL with peripheral neuropathy. In this study 16 (35.5%) patients had history of HTN, 20(44.4%) had BMI >27.5Kg/m^2, 9 (20%) had BMI of 23-27.5Kg/m^2. This observation also suggested that BMI>23kg/m^2 is an indicator for the development of prediabetes as described by Gregory A. Nicholas et al.(16) Out of 7 patients with peripheral neuropathy 4 were obese and 5 were overweight, suggesting association of higher BMI with risk of peripheral neuropathy in prediabetes. In this study, frequency of peripheral neuropathy in IGT was 17% and 16.1 % in IFG group. Bonadonna R et al, and metascreen investigators described association of metabolic syndrome with increased neuropathy in subjects of Diabetes, in this study 7 out 9 patients with peripheral neuropathy had metabolic syndrome.(17)

Nikhil Rathi compared NCV and CMAP of pre diabetic patients with controls.(18) CMAP and NCV were both lower in pre diabetic group. In this study there were no controls to compare but NCV and CMAP of patients with peripheral neuropathy were compared with patients without peripheral neuropathy, we found that CMAP and NCV both were lower in first group.Peripheral neuropathy can occur in prediabetes though it is difficult to confirm it. Most common presentation is small fiber neuropathy which can be diagnosed on the basis of history and examination.

CONCLUSION:
Our observational study demonstrates prevalence of peripheral neuropathy in pre-diabetes. Our study also demonstrates its prevalence of clinical presentation and also evident its identification by clinical examination. There is a need to develop risk-stratification tools to identify those most at risk of peripheral neuropathy. Future clinical trials are needed to explore the potential benefits of early interventions with novel pharmacotherapy, dietary and weight loss interventions, such as low-calorie diets and multifactorial risk factor modification, in this at-risk population. Early diagnosis of peripheral neuropathy in prediabetes, risk stratification and prompt management may limit the morbidity and mortality of the complications due to T2DM.

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