

## Original Research Article

# Frequency of peripheral neuropathy in pre diabetics in sub Himalayan region: a cross sectional observational study

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### ABSTRACT

**Background:** Peripheral neuropathy in pre diabetics has been studied in various studies till now. Many are in support and many against. No data was available in any study using all three criteria i.e. impaired fasting glucose, impaired glucose tolerance and HbA1C. Aim was to study the frequency of peripheral neuropathy in pre diabetics in a tertiary health care centre in sub Himalayan region.

**Methods:** 50 patients of prediabetes were enrolled for this study; preformed proforma was used to collect the information, data on examination and investigations. Then these patients were subjected to nerve conduction studies.

**Results:** Out of total 50 pre diabetic patients 9(18%) were diagnosed having peripheral neuropathy. Maximum number of pre diabetic patients were (26) in the age group 46-55 years with mean age of 44.49 years  $\pm$ 7.01 (S.D.). 28 (56%) were males with a female to male ratio of 1:1.27. 20% patients had complaint of polyuria, 12% presented with polydipsia, 14% of total pre diabetic patients had paresthesia on history. 6% patients had impaired vibration and position sense on clinical examination. Out of total 9 patients having evidence of Peripheral Neuropathy 6 (66.66%) were meeting all three criteria for Prediabetes while 8 (88.88%) had IFG, 7 patients had IGT. 42% of the patients were fulfilling the criteria of metabolic syndrome. 28 had raised TGs and out of them 5 (17.8%) had peripheral neuropathy. Out of 24 obese patients, 4 (16.6%) had peripheral neuropathy. Out of 9 patients with peripheral neuropathy 66.66% patients were considered to be suffering with peripheral neuropathy on the basis of sensory symptoms and 33.33% were considered on the basis of impaired vibration and position sense on examination, one patient diagnosed on the basis of nerve conduction studies. 38% were in high risk group of developing T2DM in future as per Indian diabetes risk score. 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 though it is difficult to confirm it. Most common is small fiber neuropathy which can be diagnosed on the basis of history and examination. But by diagnosing it early in the course of prediabetes, morbidity and mortality secondary to neuropathy can be prevented.

**Keywords:** Neuropathy, Prediabetes

### INTRODUCTION

Prediabetes is a precursor stage of Type 2 Diabetes Mellitus (T2DM). Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are collectively called as

pre diabetic states and have a high risk of progression to diabetes. South Asians appear to be prone to develop T2DM and Prediabetes at a younger age and at a lower BMI.<sup>1</sup>

### **Epidemiology and time trends**

The International Diabetes Federation (IDF) estimates that the total number of diabetics to be around 40.9 million in India.<sup>2</sup> It was estimated that there were about 77.2 million people with Prediabetes in India as of 2011.<sup>3</sup> Prediabetes is a high-risk state for DM with annualized conversion rate of 5-10% and similar percentage converting back to normal.

### **Natural history of T2DM**

In natural history of T2DM, there are various stages like normal glucose tolerance (NGT), Prediabetes, clinical diabetes and stage of complications. Effective strategies can be planned once we understand the natural history of this disease. Beta cell dysfunction and insulin resistance are the major factors responsible for this disease.

Individuals with a parent with Type 2 Diabetes Mellitus have increased risk of developing T2DM or Prediabetes. But if both parents are diabetic then the chances of developing T2DM are 40%.<sup>4</sup> This disease is polygenic and multi factorial, as it is affected not only by the genetic susceptibility but also by many environmental factors and the in utero environment.<sup>4</sup>

### **Diagnosis**

Prediabetes is diagnosed when one of following criteria is fulfilled.<sup>5</sup>

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/m<sup>2</sup>) or have additional risk factors.<sup>6</sup>

### **Complications of prediabetes and T2DM**

Morbidity and mortality in DM is related to its micro vascular and macro vascular complications. Early identification of at risk individual using simple screening tools like Indian diabetes risk score (IDRS) can be beneficial.<sup>7</sup>

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.

### **Peripheral neuropathy**

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.<sup>8</sup>

### **Clinical presentation**

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.<sup>9</sup> 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.<sup>9</sup>

### **Risk factors for peripheral neuropathy**

Various risk factors increase predisposition i.e. hyperglycemia, constitutional factors like height, nerve length, age, alcohol consumption and smoking may influence the risk of Peripheral Neuropathy. Hypertriglyceridemia and hypertension may also be the risk factors. Both myelinated and unmyelinated nerve fibers are lost. It can present as polyneuropathy, mononeuropathy or autonomic neuropathy.<sup>9</sup>

### **Presentation of peripheral neuropathy**

Polyneuropathy and mono neuropathy- most common form is distal symmetric polyneuropathy, and present as distal sensory loss and pain. Hyperesthesia, paresthesia and dysesthesia may also occur. Symptoms may occur as tingling, numbness, sharpness or burning that begins in feet and then progresses proximally in gloves and stockings distribution. Pain typically affects lower limbs and aggravates at night.

It may also manifest as polyradiculopathy, mononeuropathy, plexopathy or autonomic neuropathy. Predominantly small fiber involvement results in pain, dysesthesias, numbness whereas the predominantly large fiber involvement results in numbness, unsteady gait and loss of balance.

### **Incidence**

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.

### **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.<sup>10</sup>

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.<sup>11</sup>

### METHODS

The study was conducted in patients presenting to the Medical OPD and Medical ward. Institutional Ethical committee clearance was taken. The patients who were of age >18 years and <55 years and were natives of this area 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.

An 50 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.

### Statistical analysis

Data was recorded on a Microsoft Excel spreadsheet. All discrete variables were expressed as percentages. Statistical analysis was performed using Epi Info2000 and SPSS student version 16.0 (SPSS Inc, Chicago, USA). All discrete variables were expressed as percentages.

### RESULTS

This prospective observational study included a total number of 50 patients with a diagnosis of prediabetes, out of which 9 (18%) were found to be suffering from

peripheral neuropathy (Table 1). The age group for study ranged from 18 to 55 years with a mean age of 44.49 years  $\pm$ 7.01 (S.D.). Maximum number of patients were 26 (52%) in the age group of 46-55 years (Table 2). 56% patients were males (Table 3). Majority patients (84%) belonged to rural background (Table 4). 28 (56%) patients were doing exercise or strenuous activity, 16 (32%) moderate activity and 6 (12%) were doing sedentary activity on the basis of history (Table 5).

An 14 (28%) patients had family history of diabetes (T2DM) (Table 6). 7 (14%) patients had paresthesia, 10 (20%) had polyuria, and 6 (12%) patients had polydipsia on history (Table 6). 17 (34%) patients had BMI between 23-27.5, 24 (48%) had BMI >27.5kg/m<sup>2</sup> (Table 6).

**Table 1: Distribution of peripheral neuropathy in prediabetic patients.**

Prediabetic patients	n=50	%
Total number of patients diagnosed with peripheral neuropathy	9	18
Total number of patients without neuropathy	41	82

**Table 2: Age group distribution of prediabetes and peripheral neuropathy.**

Age groups (years)	Prediabetic		Peripheral neuropathy	
	n=50	%	n=9	%
18-25	0	0	0	0
26-35	07	14	2	22.22
36-45	17	34	4	44.44
46-55	26	52	3	33.33

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

Distribution of sex	Prediabetics		Peripheral neuropathy	
	n=50	%	n=9	%
Male	28	56	5	55.55
Female	22	44	4	44.44

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

Distribution	Prediabetes patients		Peripheral neuropathy	
	n=50	%	n=9	%
Rural	42	84	7	77.77
Urban	08	16	2	22.22

Out of total 9 patients with peripheral neuropathy 4 had BMI 23-27.5 and 4 had BMI >27.5kg/m<sup>2</sup> (Table 6). 3 patients had impaired vibration and position sense, rest all had normal sensory and motor examination (Table 6). 38 patients were fulfilling all the three criteria i.e. IFG, IGT and HbA1C between 5.7-6.4% (Table 7).

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

Physical activity	Pre diabetics		Urban dwelling	
	n = 50	%	n=8	%
Exercise or strenuous work	28	56	1	12.5
Moderate physical activity at work/home	16	32	4	50
Sedentary work and no exercise	6	12	3	37.5

**Table 6: Characteristics of pre diabetics.**

Symptoms	Prediabetes	
	n =50	%
Paresthesia	07	14
Weakness	00	00
Polyuria	10	20
Polydypsia	06	12
Polyphagia	00	00
HTN	14	28
CVD	1	2
Family history of T2DM	14	28
Smoker	6	12
Waist circumference>90 cm in males and >80 cm in females	48	96
Fasting TG >150mg/dl	28	56
Metabolic syndrome	41	82
Vibration and position impaired	3	6
Touch, pain or temperature impaired	0	0
BMI 23-27.5	14	34
BMI>27.5	24	48

**Table 7: Distribution of glycemic status of all patients.**

Glycemic status	Prediabetics		Peripheral neuropathy	
	n=50	%	Present	%
Impaired FBG	49	98	8	16.1
IGT	41	82	7	17.0
HbA1C (5.7-6.4%)	48	96	9	18.7
IFG+IGT	40	80	6	15.0
IFG+HbA1C (5.7-6.4%)	47	94	8	17.0
IGT+HbA1C (5.7-6.4%)	39	78	7	17.9
IFG+IGT+HbA1C (5.7-6.4%)	38	76	6	15.7

Out of total 50 patients 41(82%) were fulfilling criteria for metabolic syndrome and out of 9 patients with peripheral neuropathy 7 were diagnosed with metabolic syndrome (table no.06). Mean Compound motor action potential (CMAP) of patients with peripheral neuropathy was 5.5 mV in comparison to 12.39 mV in the patients

without peripheral neuropathy (Table 7). While mean nerve conduction velocity (NCV) of patients with peripheral neuropathy was 45.5m/s in comparison to 46.9m/s in patients without peripheral neuropathy.

**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

This prospective observational study included a total number of 50 patients of prediabetes, who presented to the department of medicine 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 50 patients 9 (18%) 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.<sup>12</sup> 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.<sup>13</sup> In this study, we had no controls and T2DM patients for comparison, but frequency of peripheral neuropathy was 18%, though methods of diagnosing peripheral neuropathy were different in this study. It is higher than the prevalence reported by previous studies though our sample size was smaller in comparison to these studies.

Maximum patients were in the age group of 46-55 years, as expected as incidence of diabetes increases with age. In this study 14% patients had paresthesia, 20% had polyuria and 12% had polydypsia. We could not find such data for comparison in literature. In this study out of 50 patients 28 (56%) were doing exercise or strenuous activity, 16 (32%) were doing moderate activity and 6 (12%) 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 14 (28%) patients had history of HTN, 24 (48%) had BMI >27.5Kg/m<sup>2</sup>, 17 (34%) had BMI of 23-27.5Kg/m<sup>2</sup>. This observation also suggested that BMI

>23kg/m<sup>2</sup> is an indicator for the development of prediabetes as described by Gregory A. Nicholas et al.<sup>14</sup> Out of 9 patients with peripheral neuropathy 4 were obese and 4 were overweight, suggesting association of higher BMI with risk of peripheral neuropathy in prediabetes. Frequency of peripheral neuropathy in pre diabetics with raised TGs was 17.8%. Dan Ziegler described prevalence of peripheral neuropathy in IGT as 13%, IFG 11.3%, 7.4% in NGT.<sup>4</sup> 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 of 9 patients with peripheral neuropathy had metabolic syndrome.<sup>15</sup>

Nikhil Rathi compared NCV and CMAP of pre diabetic patients with controls.<sup>16</sup> 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.

## CONCLUSION

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. Nerve conduction studies are not able to diagnose subclinical neuropathies though CMAP and NCV in patients with neuropathy were less than in comparison to patients without neuropathy, so we need better modalities for this purpose. But by diagnosing it early in the course of prediabetes, morbidity and mortality secondary to neuropathy can be prevented. More than half the patients had high risk Indian diabetes risk score, so a high risk of developing diabetes in future and also peripheral neuropathy.

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