Original Research Article

A cross sectional study of insulin resistance as a predictor of sensory neuropathy in patients with prediabetes

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Abstract

Background: Prediabetes represents the earliest stage of glucose dysregulation, and precedes the development of overt type 2 diabetes. Insulin resistance is defined as a state of decreased responsiveness of target tissues to normal circulating levels of insulin and is the central feature of type 2 diabetes and Metabolic Syndrome. Present study was aimed to study insulin resistance as a predictor of sensory neuropathy in prediabetes. **Material and Methods:** Present study was hospital based, prospective, observational study conducted in patients of age of 40–60 years, with prediabetic status as defined by the American Diabetes Association (Fasting plasma glucose between 100 and 125 mg/dL or 2-h postprandial plasma glucose between 140 and 199 mg/dL or glycated hemoglobin 5.7%–6.4%). We measured fasting serum Insulin levels and vibration perception thresholds (using Digital Biothesiometer). **Results:** In present study, 50 prediabetic cases were studied. According to VPTs, 7 cases had peripheral neuropathy (14 %). Majority of neuropathy cases were from 51-60 years age (12 %). Age and gender were comparable among total cases and cases with peripheral neuropathy and difference was not statistically significant ($p>0.05$). Raised values of Serum insulin (mIU/L) and HOMA IR (Homeostatic model assessment of insulin resistance) were noted among cases with peripheral neuropathy as compared with total cases and difference was statistically significant ($p<0.05$). VPTs were found to have statistically significant positive correlation with fasting serum insulin levels and HOMA-IR in both feet. **Conclusion:** VPTs were found to have statistically significant positive correlation with fasting serum insulin levels and HOMA-IR and thus insulin resistance can be used as a predictor of sensory neuropathy in patients with prediabetes.

Keywords: sensory neuropathy, prediabetes, diabetes, Insulin resistance

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INTRODUCTION

Peripheral neuropathy (PN) is a prevalent disorder of the peripheral nervous system, which may be associated with varying combinations of weakness, autonomic changes, and sensory changes.[1] Peripheral neuropathy is a serious complication of diabetes. It plays a major contributory role in the initiation of foot ulceration and the subsequent development of lower extremity amputation, resulting in severe disability, reduced quality of life, and a significant economic burden to the health care system.[2] Prediabetes represents the earliest stage of glucose dysregulation, and precedes the development of overt type 2 diabetes. Prediabetes can be divided into impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). A fasting plasma glucose of 100–125 mg/dL (5.6–6.9 mmol/L) defines IFG, and a 2-h oral glucose of 140–199 mg/dL (7.8–11.0 mmol/L) defines IGT.[3] Observational evidence suggests an association between prediabetes and complications of diabetes such as nephropathy, small fiber neuropathy, early retinopathy and risk of macrovascular

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disease.[4] Reason for the rate of increase of complications may be lack of observation is regular follow-up programmes and unawareness about the conditions of disease. In the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) study, "diabetic" polyneuropathy was approximately twice that of normal subjects in those with IFG and IGT, whereas it was doubled again in patients with diabetes.[5] Insulin resistance is defined as a state of decreased responsiveness of target tissues to normal circulating levels of insulin and is the central feature of type 2 diabetes and Metabolic Syndrome. Present study was aimed to study insulin resistance as a predictor of sensory neuropathy in prediabetes.

MATERIAL AND METHODS

Present study was hospital based, prospective, observational study conducted in Department of Medicine, Maharashtra Institute of Medical Sciences and Research, Latur, India. Study was conducted during January 2020 to December 2020. Study approval was taken from institutional ethical committee.

Inclusion criteria: Patients of age of 40–60 years, with prediabetic status as defined by the American Diabetes Association (Fasting plasma glucose between 100 and 125 mg/dL or 2-h postprandial plasma glucose between 140 and 199 mg/dL or glycated hemoglobin 5.7%–6.4%).

Exclusion criteria: Patients with history of cerebrovascular accidents, receiving drugs known to cause neuropathy (AKT, chemotherapy and/or radiotherapy, antiretroviral drugs). Patients with malignancy, diagnosed hypothyroidism, chronic alcoholics, chronic smokers, systemic lupus erythematosus, leprosy, vasculitis, neurological disorders such as Guillain-Barré syndrome, multiple sclerosis. Patients not willing to participate in study.

Study was explained and a written informed consent was taken. Cases were selected from patients attending OPDs or admitted for some other reasons in wards and considered for present study only after confirmation of reports. Demographic data, general history, past medical/surgical history was taken and examination findings were noted. We measured fasting serum Insulin levels (by using the enzyme-linked immunosorbent assay kit) and basal state insulin resistance of the individual was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR). Vibration perception thresholds (VPTs) were measured using Digital Biothesiometer (Vibrotest) using the PLANTAR method, and the average value was calculated in both feet. Patients with average VPT of >15 V on either side were considered to have neuropathy. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. The Pearson's correlation coefficient was calculated to assess the correlation between two continuous variables. P value less than 0.5 was considered as statistically significant.

RESULTS

In present study, 50 prediabetic cases were studied. According to VPTs, 7 cases had peripheral neuropathy (14 %). Majority of neuropathy cases were from 51-60 years age (12 %). Age and gender were comparable among total cases and cases with peripheral neuropathy and difference was not statistically significant (p>0.05).

Table 1: Age and gender distribution

Characteristic	Total cases (n=50) (%)	Peripheral neuropathy (n=7) (%)	P value
Age groups (years)			0.065
41-50	21 (42 %)	1 (2 %)	
51-60	29 (58 %)	6 (12 %)	
Mean Age (years)	54.68 ± 7.27	57.56 ± 6.77	0.051
Gender			0.073
Male	30 (60 %)	4 (8 %)	
Female	20 (40 %)	3 (6 %)	

Raised values of Serum insulin (mIU/L) and HOMA IR (Homeostatic model assessment of insulin resistance) were noted among cases with peripheral neuropathy as compared with total cases and difference was statistically significant (p<0.05).

Table 2: Comparison of biochemical parameters in patients with or without neuropathy

Characteristic	Total case (n=50) (%)	Peripheral neuropathy (n=7) (%)	P value
Serum insulin (mIU/L)	8.91 ± 3.74	11.98 ± 4.36	0.025
HOMA IR	2.01 ± 1.21	3.43 ± 1.28	0.002

VPTs were found to have statistically significant positive correlation with fasting serum insulin levels and HOMA-IR in both feet.

Table 3: Correlation of vibration perception thresholds with fasting serum insulin levels and HOMA-IR

Correlation Indices	Corresponding values (on Right foot)	Corresponding values (on left foot)
Serum insulin (mIU/L)		
Pearson correlation	0.294	0.321
Significant (two-tailed)	0.03	0.02
HOMA IR		
Pearson correlation	0.301	0.293
Significant (two-tailed)	0.03	0.019

DISCUSSION

Prediabetes is increasingly recognised as an important metabolic state; as well as predisposing individuals to a high probability of future progression to diabetes, individuals with prediabetes are at increased risk of developing many of the pathologies normally associated with that disease, such as diabetic retinopathy, neuropathy, nephropathy and macrovascular complications.[6] The neuropathy observed in patients with diabetes consists of several changes: demyelination, axonal thickening, and loss of nerve fibers. In diabetes, hyperglycemia appears to be the dominant cause of these changes, and presumably, intermediate hyperglycemia can account for more cases of neuropathy seen in patients with pre-diabetes.[7] Impaired glucose tolerance (IGT)/ prediabetes is a marker of insulin resistance and is predictive of microvascular and macrovascular complications , irrespective of progression to diabetes.[8] Diabetic Neuropathy (DN) is defined as 'the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes'. [9] The spectrum ranges from a mild sensory disturbance as can be seen in most common form i.e. diabetic sensorimotor polyneuropathy (DSPN), to the debilitating pain and weakness of a diabetic lumbosacral radiculoplexus neuropathy. Lee CC *et al.*,[10] studied 467 individuals in the longitudinal PROMISE (Prospective Metabolism and Islet Cell Evaluation) cohort, prevalence of peripheral neuropathy was 29%, 49%, and 50% for normal glycemia, prediabetes, and new-onset diabetes, respectively (P < 0.001 for trend). The mean VPT was 6.5 V for normal glycemia, 7.9 V for prediabetes, and 7.6 V for new-onset diabetes (P = 0.024 for trend). Prediabetes was associated with higher MNSI scores (P = 0.01) and VPTs (P = 0.004) versus normal glycemia, independent of known risk factors. Additionally, progression of glucose intolerance over 3 years predicted a higher risk of peripheral neuropathy (P = 0.007) and nerve dysfunction (P = 0.002). Prediabetes, but not metabolic syndrome, was independently associated with both the presence of peripheral neuropathy and the severity of nerve dysfunction Singh A *et al.*,[11] studied 60 prediabetic cases, the age distribution ranged from 35 years to 60 years with the mean age of 48.68 years. Male and female formed 65% and 35% of the study population, respectively. The maximum fasting serum insulin levels were 21.8 mIU/L, and the minimum fasting serum insulin levels were 3.5 mIU/L, with the mean value being 10.61 ± 4.99 mIU/L. The maximum HOMA-IR was 6.4, and the minimum was 0.986, with the mean value being 2.81 ± 1.37. Among all the prediabetic patients, 43.3% of patients had neuropathy. T-test analysis suggests that mean fasting serum insulin levels (P = 0.026) and HOMA-IR (P = 0.032) were significantly higher in patients with neuropathy than patients without neuropathy. VPTs were found to have statistically significant positive correlation with fasting serum insulin levels and HOMA-IR. Similar findings were noted in present study. Khursheed Alam *et al.*,[12] studied 60 prediabetic cases, mean age was 48.68 years. In selected subject males were 65% whereas the females were 35%. The minimum level of fasting insulin serum was 3.5 mIU/L whereas the maximum level of fasting serum insulin was 21.8 mIU/L and the mean value was 10.61 ± 4.99 mIU/L. The minimum HOMA-IR was 0.986 and the maximum of it was 6.4 whereas the mean value of it was 2.81 ± 1.37. Using digital Biothrsiometer, according to VPT measured around 43.3% patients had neuropathy. In patients with neuropathy as compared to the patients without neuropathy HOMA-IR (P=0.032) and serum insulin level (P=0.026) was significantly higher. There was significant positive relation found of VPT with HOMA-IR IR (Pearson correlation coefficient = 0.299 [R], 0.281 [L]; P = 0.02 [R], 0.03 [L]) and fasting insulin serum level levels HOMO-IR, quantified with the help of index and insulin resistance are correlated with the development of sensory neuropathy. Similar findings were noted in present study. In a comparative study with 65 cases (prediabetic) and 65 controls, compound muscle action potential (CMAP) and nerve conduction velocity (NCV) of right tibial nerve were significantly reduced in the cases as compared to controls and were found to be statistically significant suggesting motor axonal neuropathy. The sensory nerve action potential (SNAP) and NCV of right sural nerve were significantly reduced in the cases as compared to controls which were found out to be statistically significant suggesting that cases had sensory axonal neuropathy.[13] Other studies show that patients with MetS and prediabetes have an elevated risk of cryptogenic sensory polyneuropathy (CSPN) before the onset of frank

diabetes, and that CSPN patients have an elevated risk of MetS and its component metabolic abnormalities.[14] Individual risk factors for diabetes (such as history of gestational diabetes, first degree relative with diabetes) or a combination of risk factors (e.g. metabolic syndrome) can also be used to define populations at-risk for diabetes but their predictive value is poorer than that of prediabetes.[15] 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.

CONCLUSION

VPTs were found to have statistically significant positive correlation with fasting serum insulin levels and HOMA-IR and thus insulin resistance can be used as a predictor of sensory neuropathy in patients with prediabetes.

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