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"ASSOCIATION BETWEEN NERVE CONDUCTION VELOCITY WITH INSULIN RESISTANCE IN PREDIABETICS AND HEALTHY CONTROLS"

Physiology

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ABSTRACT

Background: Prediabetics are known to have IR and studies suggests that hyperinsulinemia induced IR causes the neurons to undergo degeneration which contributes to the development of peripheral neuropathy. The objective of the present study was to establish an association between Nerve conduction velocity (NCV) and Insulin resistance (IR) in prediabetics as compared to healthy controls.

Material and methods: Twenty six prediabetic subjects (diagnosed as per 2010 ADA guidelines) between 40 to 65 years of age in both sex and twenty six controls (age, gender, BMI matched) were enrolled for the study. Blood samples were collected for measuring fasting blood sugar (FBS) and fasting insulin (FI) level. IR was calculated using HOMAIR index. NCV was recorded on Schwarzer Topas EMG – 4channel EMG/NCV/EP – system for all the subjects. Statistical analysis was performed using SPSS version 21 software and a p value of <0.05 was considered statistically significant.

Results: There was a significant reduction in NCV of bilateral peroneal nerve ($p<0.001$) and sural nerve ($p<0.001$) in prediabetics as compared to controls. A significant negative association was also obtained between IR and NCV of bilateral peroneal & left sural nerve.

Conclusion: The results obtained in our study indicates that with increase in insulin resistance there is delay in nerve conduction in motor and sensory nerves in prediabetics.

KEYWORDS

Insulin Resistance, Peripheral Neuropathy, Prediabetics.

INTRODUCTION:

Prediabetes as the name indicates, a stage before type 2 diabetes mellitus (T2DM) with either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or both IFG and IGT [1].-Across the world, the prevalence of prediabetes may rise to 470 million by 2030 which is currently now 371 million.[2,3] In India, approximately 77.2 million were found to have prediabetes.[4-6]

Population having impaired fasting glucose levels have been considered as a risk group for the future development of diabetes and peripheral neuropathy.[7] The prevalence of peripheral neuropathy was found to be 11-25% among prediabetics and nearly 25% to 62% of the individuals with idiopathic peripheral neuropathy were found to be prediabetics.[8] Forsblom et and Abbott el has reported that Peripheral neuropathy could be an independent risk factor for morbidity[9] and mortality.[10]

Insulin resistance (IR)[11] is estimated using Homeostatic model assessment and insulin resistance (HOMA-IR) method, it assesses the β-cell function and IR from fasting blood glucose (FBS) and insulin or C-peptide concentrations.[12] Fasting insulin (FI) concentration was found to be twofold higher in prediabetics subjects.[13] Increased lipid oxidation[14] and hyperinsulinemia caused by short-time B-cell stimulation with free fatty acids worsens the insulin resistance.[15,16]

Although many studies were done on diabetic patients there were very few studies on peripheral nerve conduction along its correlation with insulin resistance among prediabetics in India. Hence, the present study was aimed to document nerve conduction and to study its association if any, with insulin resistance among prediabetics.

Material and Methods:

Study sample:

Twenty six prediabetic subjects in 40 to 65 years of age of both genders and twenty six apparently healthy controls (age, sex and BMI matched) were enrolled for the study based on fasting blood sugar (FBS) level as per ADA guidelines[17] According to this, the subjects with FBG between 100 to 125mg/dl were designated as prediabetics and subjects with FBG less than 100mg/dl were considered as healthy controls, their glucose tolerance and glycated haemoglobin levels were within normal range. Study participants were recruited from General Medicine department on out-patient basis using predetermined eligibility criteria.

Institutional ethical committee clearance was sought and obtained before the commencement of the study. Subjects fulfilling inclusion criteria were enrolled for study. All the procedures were clearly explained to study participants beforehand. Subjects with anemia, diabetes Mellitus, hepatic or renal diseases, spinal injury or spinal diseases and seriously ill patients were excluded from the study. Subjects who were chronic alcoholics and those on any medications like steroids, oral hypoglycemic, phenytoin were also excluded from the study. General physical examination and anthropometric measurements were taken on all the study participants. Later, they were instructed to come to Dept. of Physiology, for the biochemical and nerve conduction recording.

Biochemical analysis:

Blood samples were collected from antecubital vein in fasting state and sent to biochemistry lab for biochemical analysis for estimating FBS and FI level. FBS and FI were measured using spectrophotometry by

glucose oxidase method and electro-chemiluminescence method. HOMA IR was calculated using the following formula:[18] FBS (mg/dl) x FI (μU/mL) / 405

Recording of NCV:
Nerve conduction velocity was recorded on bilateral peroneal and sural nerves using Schwarzer Topas EMG – 4channel EMG/NCV/EP – system by Natus Europe GmbH machine.

Peroneal NCV:
The subjects were asked to lie down in supine position and both legs were cleaned using spirit swabs. A pair of recording electrodes having one active (G1) electrode placed on the belly of Extensor digitorum brevis muscle and one reference (G2) electrode on the tendon of same muscle, (ie) on the base of 5th little toe and the ground electrode was tied around the calf muscle. All the electrodes were placed in position with the help of conducting paste.[19,20] The propagated muscle action potential, originating under G1 located near the motor point, gives rise to a simple biphasic waveform with an initial negativity. Then NCV were recorded by giving stimulus intensity from 30-100mA. Motor (Peroneal) NCV was calculated using a formula: Nerve conduction velocity= distance/ (proximal latency – distal latency).[21]

Sural NCV:
The subjects were asked to lie down in prone position and lateral aspect of both feet were cleaned using spirit swabs. Active electrode was placed behind and below the lateral malleolus, reference electrode was placed 3cm away from active electrode towards the little toe. Ground electrode was tied around the calf muscle. Stimulation, ranging from 11 to 18mA current was given 14cm away from the lateral malleolus on the posterior part of leg towards knee joint with the help of surface stimulator.[20-22] Sural NCV requires stimulation at a single point, hence only onset latencies were used to calculate using a formula: Sensory conduction velocity = distance /onset latency.

Statistical analysis: Statistical analysis was performed by using SPSS version 21 software. The data obtained was not normal in distribution after applying the normality distribution test. Mann-Whitney test was applied for comparison among the two groups and Spearman correlation co-efficient test was applied for correlation analysis. Chi square test was applied to test statistically significant difference in proportions.

Results:

Table 1: Comparison tables showing demographic data and NCV among prediabetic and control group:

Parameters		Controls (n=26)	Prediabetics (n=26)	p Value
		(Mean ± SEM)	(Mean ± SEM)	
Age(years)		46.38 ± 1.41	45.77 ± 1.27	0.742
Gender¶	Male	09	10	1.000
	Female	17	16	
BMI(kg/m^2)		23.85 ± 0.49	24.60 ± 0.47	0.197
FI (μIU/dl)		9.20 ± 1.03	16.94 ± 2.56	**0.005**
FBS (mg/dl)		86.65 ± 1.39	105.96 ± 2.41	**0.000**
HOMA IR		1.98 ± 0.24	4.34 ± 0.66	**0.001**
Right peroneal NCV (ms)		51.67 ± 1.27	44.40 ± 0.92	**<0.001**
Left Peroneal NCV (ms)		52.36 ± 1.33	43.64 ± 1.41	**<0.001**
Right sural NCV (ms)		55.11 ± 2.18	42.37 ± 1.85	**<0.001**
Left sural NCV (ms)		56.28 ± 1.54	41.75 ± 1.99	**<0.001**

p>0.05-Non-Significant, p < 0.05 - Significant, p <0.01 - Highly Significant, p < 0.001 - Very Highly Significant. ¶Chi square test.

Table 1 illustrates the demographic data with age, sex and BMI matched, hence both the groups were comparable and also illustrated the nerve conduction velocity between two groups.

Table 2: Correlation analysis between Insulin resistance (HOMAIR) and NCV in a pooled data (n=52):

Nerve conduction velocity(ms)	FBS (mg/dl)		FI (μIU/dl)		HOMAIR	
	R	p	R	p	R	p
Right Peroneal Nerve	-0.255	0.068	-0.389	**0.004**	-0.379	**0.006**
Left Peroneal nerve	-0.382	**0.005**	-0.399	**0.003**	-0.426	**0.002**
Right Sural Nerve	-0.374	**0.006**	-0.189	0.179	-0.225	0.109
Left Sural Nerve	-0.522	**0.000**	-0.206	0143	-0.285	**0.041**

p>0.05-Non-Significant, p < 0.05 - Significant, p <0.01 - Highly Significant, p < 0.001 - Very Highly Significant.

Table2 illustrates the significant association between HOMAIR and NCV of peroneal and sural nerves.

Discussion:
The present study was carried out among prediabetics to determine the NCV changes on bilateral peroneal and sural nerve, the other objective was to observe its association with IR.

Nerve conduction velocity were significantly lower on both side peroneal nerves (p<0.001) and bilateral sural nerve (p<0.001) in prediabetics as compared to controls (Table 1). Our results were in agreement with the results of study done by Devi et al,[23] which showed a significant decrease in conduction velocity of peroneal and sural nerve in prediabetes. Their study supported the importance of the nerve conduction in prediabetes for early detection of neuropathy In Burke et al[24] study, the changes in sural nerve conduction was prominent as compared to median sensory and hence they concluded that the sural sensory nerve conduction was the single most useful test in the diagnosis of sensory polyneuropathy.

Preferential injury to small unmyelinated nerves as suggested by prominent neuropathic pain, predominant sensory injury were considered as an early complications of T2DM.[25] The demonstration of neuropathic dysfunction in prediabetics emphasizes the susceptibility of peripheral nerve fibres, especially small A delta fibres and C fibres, to relatively mild, short-duration hyperglycemic changes.[26] From the present study it was evident that the prediabetic population were having derangement in motor and sensory peripheral nerve conduction. Insulin, a neurotropic factor responsible for the regulation of neuronal growth, survival and differentiation.[27,28] In conditions like hyperinsulinemia-induced IR, these neurons may cause injury to peripheral and central nervous systems.[29]

Our study also demonstrated a significant inverse association between FBS and NCV of B/L sural nerve and left peroneal nerve. Fasting insulin showed a significant negative correlation only with peroneal nerve conduction and not with sural NCV. A significant inverse association was obtained between HOMAIR, B/L peroneal NCV and left sural NCV (Table 2). This negative association between insulin resistance and NCV in both motor and sensory nerve could point towards a possible role of insulin resistance in pathogenesis of nerve conduction derangement. It has also been proposed that oxidative stress[30] and hyperinsulinemia induced IR causes the neurons to undergo degeneration which further contributes to the pathogenesis of diabetic neuropathy.[29]

Hence, the present study suggests that the increase in insulin resistance in prediabetics may be linked or associated with development of peripheral neuropathy. The study also brings out the importance of performing nerve conduction test in prediabetic individuals who may develop peripheral neuropathy even before frank diabetes sets in. The only possible limitation for the present study could be a small sample size. An elaborated study with larger sample size can be conducted in future among these population and the early lifestyle intervention recommended in the form of counselling sessions, dietary modification, regular exercise and yoga in prediabetics may help in preventing the development of diabetes mellitus and its complications.

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