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Original Article

Physiology Section

Study of Electrophysiological Changes in Sensory Nerves Among Diabetic Smokers

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ABSTRACT

Introduction: Neuropathy is one of the most troublesome complication affecting individuals with diabetes. The resultant loss of function in peripheral nerves causes loss of protective sensations and impairs patient's ability to perceive incipient or even apparent ulcerations in the feet.

Aim: This study was undertaken to test the hypothesis of alteration in electrophysiological parameters of nerve before actual manifestations of neuropathy in type 2 diabetic patients and to analyse the effect of smoking on Sensory Nerve Conduction Velocity (SNCV) of diabetic subjects.

Materials and Methods: One hundred and twenty diagnosed diabetics were taken as cases while 30 healthy non diabetics were taken as control. Case group was divided into diabetic non-smoker and diabetic smoker. Diabetic smoker were further subdivided into light smoker, moderate smoker and heavy smoker according to smoking index. After detailed history and physical examination SNCV of median and ulnar nerve in upper limb and sural nerve in lower limb was performed.

Results: On comparison of SNCV of median and ulnar nerve of upper limb and sural nerve of lower limb between control and diabetic non-smoker only sural nerve of diabetic non smoker showed significant bilateral decrease. There was significant bilateral decrease in SNCV of median and ulnar nerve of diabetic heavy smoker when compared to control and diabetic non smoker. Similarly, SNCV of sural nerve of diabetic heavy smoker was significantly decreased when compared with control, diabetic non-smoker, diabetic light and moderate smoker. A negative and statistically significant correlation was found between SNCV and smoking index.

Conclusion: Present study indicates that nerves of lower limbs are more susceptible to diabetic assault as compared to upper limb suggesting that long nerves are commonly affected. Also, apart from duration and severity of diabetes, smoking itself is an independent factor for diabetic neuropathy.

Keywords: Cigarette smoking, Diabetes, Diabetic polyneuropathy, Sensory nerve conduction velocity, Smoking index

INTRODUCTION

Diabetes mellitus (DM) is one of the leading health problem of South Asian region and it's prevalence would rise over 151% between 2000 and 2030 [1]. Among various complication of diabetes, diabetic neuropathy is considered one of the most commom micro-vascular complication of both type I and II DM. However, despite being an important and common complication it has not been studied as extensively as macro-vascular complications e.g. Stroke, Peripheral vascular diseases and coronary artery disease [2]. It's usually evinced that neuropathy is associated with both the diabetes duration and level of hyperglycaemia, however lesser known risk factors like cigarette smoking, retinopathy, hypertension, obesity, hyperlipidaemia and microalbuminuria are still less acquainted. Cigarette smoke contains more than 4,000 different toxic and carcinogenic chemicals which have a profound direct toxic effect on the myelin sheath [3]. Smoking also results in subclinical changes of the myelin sheath which causes poor electrotonic conduction. The diagnosis of diabetic peripheral neuropathy is mainly based on its characteristic symptoms, but mostly these symptoms develop at any stage of neuropathic impairment or they may not develop at all. In many instances, it is evident that diabetic peripheral neuropathy if diagnosed earlier can be treated promptly in the initial stages [4]. This stipulated the need of performing nerve conduction studies (NCS), a common tool implied in the diagnosis of peripheral nerve disorders. Thus, keeping the aforementioned background in mind, the present study was designed to test the hypothesis of alteration in electro physiologic parameters of nerve before actual manifestations of neuropathy in type II diabetic patients appear and also to assess the effect of smoking on nerve conduction velocity in type 2 diabetic subjects.

MATERIALS AND METHODS

This case control study was conducted in the Department of Physiology, National Institute of Medical Sciences (NIMS) Medical College and Hospital, Jaipur between October 2013 and April 2015. After approval from the institutional ethical committee informed and written consent was taken from all the participants of the study. A total of 150 male subjects in the age group of 30-60 years comprising of 120 diagnosed cases of diabetes and 30 non-diabetics as control were selected. Subjects who never had any addiction related to tobacco and no history of any major illness were taken as control group. Case group was divided into diabetic non-smokers and diabetic smokers. Active smoking with the history of smoking filtered cigarettes for more than five years was taken as smokers. Diabetic smokers were further classified into light smokers, moderate smokers and heavy smokers according to smoking index [5].

Smoking index is used to find the exposure of smoking on body quantitatively and is calculated by multiplying the average number of cigarettes smoked per day in last seven days with the duration of smoking in years. As per Smoking index, smokers were classified into; Light smokers (Smoking index < 100), moderate smokers (Smoking index-101-200) and heavy smoker (Smoking index ≥ 201). The sample size for each group was calculated as 30. The formula for comparing the difference of means between the groups was used with α=0.05, power (ß) = 90% and effectivw size (es) = 0.7 which gives sample size n=28 [6]. Exclusion criteria include no previous history of any systemic condition related to peripheral neuropathy (Hypertension, malnutrition, alcoholic neuropathy, renal failure), any neuromuscular disorders such as myopathy, familial polyneuropathy or chronic polyneuropathy, GB syndrome,

Nerve	Antidromic / Orthodromic	Point of Stimulation	Point of Recording
MEDIAN	Antidromic	Wrist	Index finger
ULNAR	Antidromic	Wrist	Little finger
SURAL	Antidromic	At the junction of middle and lower 1/3rd of the leg	Ankle

[Table/Fig-1]: Detail of SNCV recordings.

Parameter		Control (n=30) M ± SD (m/s)	Diabetic Non Smoker (n=30) M ± SD (m/s)	Diabetic Light Smoker (n=30) M ± SD (m/s)	Diabetic Moderate Smoker (n=31) M ± SD (m/s)	Diabetic Heavy Smoker (n=29) M ± SD (m/s)	p-value
Median SNCV	Right	57.44± 6.68	56.04± 6.5*	55.84± 6.57*#	55.71± 6.50*#	49.83 ± 8.47**##f%	<0.05
	Left	57.32± 6.42	55.94± 6.49*	55.84± 6,57*#	55.72± 6.50*#	48.87 ± 7.22**##f%	<0.05
Ulnar SNCV	Right	56.41± 7.04	55.10± 7.00*	54.85± 6.94*#	54.76± 6.84*#	46.81 ± 9.75**##f%	<0.05
	Left	56.21± 7.13	55.02± 6.98*	54.85± 6.94*#	54.76± 6.84*#	47.05 ± 9.57**##f%	<0.05
Sural SNCV	Right	50.31± 6.65	44.42± 6.93**	44.30± 5.34**#	44.12± 5.33**#	40.29 ± 5.68**##f%%	<0.05
	Left	51.00± 6.52	46.08± 5.31**	44.44± 5.42**#	44.09± 5.70**#	40.34 ± 5.33**##f%%	<0.05

[Table/Fig-2]: Comparison of Sensory Nerve Conduction Velocity (SNCV) of various nerves between control, diabetic non-smokers and subgroups of diabetic smokers. Data was presented as mean ± standard deviation. Analysis was done using one-way ANOVA followed by post-hoc Bonferroni test. The * depicts comparison with control, # depicts comparison with diabetic non-smoker, f depicts comparison with diabetic light smoker, % depicts comparison with diabetic moderate smoker. ** p<0.05, ## p<0.05, ff p<0.05, %% P<0.05.

neuropathies associated with exogenous toxic agents, metals or drugs. Subjects with skin lesions, swelling and trauma that would interfere with Nerve Conduction Study (NCS) were also excluded. After detailed history and physical examination Sensory Nerve Conduction Velocity (SNCV) of median and ulnar nerve in upper limb and sural nerve in lower limb was performed [Table/Fig-1] in the Neurophysiology laboratory of the Department of Physiology, NIMS Medical College and Hospital, Jaipur. Medicaid System's EMG/NCV machine equipped with Neuroperfect software was used to perform nerve conduction study.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS (Statistical Package for the Social Sciences, version 17). One-way Analysis of variance (ANOVA) was used for comparing SNCV between controls, diabetic non-smoker and sub classification of diabetes smokers. Bonferroni post hoc test was used for studying multiple comparisons. Pearson correlation test was used to correlate SNCV with smoking index and simple linear regression analysis was done to predict SNCV on the basis of smoking index.

RESULTS

The sensory nerve conduction velocity (SNCV) in non diabetic and sub groups of diabetics have been shown in [Table/Fig-2]. According to [Table/Fig-2] the mean values of SNCV of median and ulnar nerves were found bilaterally decreased in diabetic non-smokers, diabetic light smokers, and diabetic moderate smokers when compared with control but statistically it was non-significant. However, there was significant bilateral decrease in SNCV of median and ulnar nerves of diabetic heavy smokers when compared with control and diabetic non-smokers. The mean values of SNCV of sural nerve of right and left lower limb in diabetic non-smokers, diabetic light smokers, diabetic moderate smokers, and diabetic heavy smokers was found significantly less when compared with control. Also, a significant bilateral decrease in SNCV of median, ulnar and sural nerve of diabetic heavy smokers was found when compared with

Sensory Nerves (Upper limb and Lower limb)		r-value
Median Sensory Nerve	Right	-0.279*
	Left	-0.394*
Ulnar Sensory Nerve	Right	-0.329*
	Left	-0.334*
Sural Sensory Nerve	Right	-0.272*
	Left	-0.293*

[Table/Fig-3]: Pearson correlation between SNCV and smoking index. Data was analysed using 'Pearson' correlation between SNCV and smoking index, 'r' representing 'Pearson' correlation coefficient. * depict 'p'<0.05

Sensory Nerves (Upper limb and Lower limb)		ß-Value	R-Square	p-value
Median Sensory Nerve	Right	-0.279	0.078	<0.05
	Left	-0.394	0.115	<0.05
Ulnar Sensory Nerve	Right	-0.329	0.109	<0.05
	Left	-0.334	0.112	<0.05
Sural Sensory Nerve	Right	-0.272	0.074	<0.05
	Left	-0.293	0.086	<0.05

[Table/Fig-4]: Simple Linear Regression Analysis for SNCV and smoking index. Data was analysed using simple linear regression for SNCV & smoking index. 'ß' representing slope of best fitted regression line; R Square representing coefficient of determination

diabetic non-smokers. There was no significant difference in SNCV of median, ulnar and sural nerve when diabetic light and moderate smokers were compared with diabetic non-smokers. Similarly, among the subgroups of diabetic smokers no significant difference in SNCV of median and ulnar nerve was seen. Further, there was no significant difference in SNCV of sural nerve between diabetic light smokers and diabetic moderate smoker in both right and left lower limb. However, the SNCV of sural nerve of diabetic heavy smokers was significantly decreased when compared with diabetic light smokers and diabetic moderate smokers. As per [Table/Fig-3], there was negative and statistically significant correlation between SNCV and smoking index. Further relationship between smoking index and SNCV was analysed using simple linear regression analysis [Table/Fig-4]. The slope of best fitted regression line ß indicates that for each increase in smoking index there was a significant decrease in SNCV of right median sensory nerve by (0.279 m/sec), left median sensory nerve (0.394m/sec), right ulnar sensory nerve (0.329 m/sec), left ulnar sensory nerve (0.334 m/sec), right sensory sural nerve (0.272 m/sec) and left sensory sural (0.293 m/sec). This supports the hypothesis of an inverse relationship between SNCV and smoking index. As per R^2 value decrease in SNCV was dependent on smoking index by 7.8%, 11.5%, 10.9%, 11.2%, 7.4% and 8.6% in media sensory nerve (right), media sensory nerve (left), ulnar sensory nerve (right), ulnar sensory nerve (left), sural sensory nerve (right) and sural sensory nerve (left) respectively.

DISCUSSION

The diabetic neuropathies include several distinctive clinical syndromes with differing clinical manifestations, anatomic distributions, and clinical courses. So apart from presence of symptoms and signs, presence of electrophysiological abnormalities have become important in the diagnosis of diabetic neuropathy [7]. Nerve conduction studies are sensitive, specific, reproducible, and easily standardized measures of the presence of nerve function impairment [8].

In the initial half of the study, SNCV was evaluated in diabetic non-smokers and compared it with healthy controls. A significant bilateral decrease in the SNCV of lower limb (sural nerve) was observed in diabetic non-smokers. However, bilateral decrease in the SNCV of upper limb (Median and Ulnar nerves) was seen in diabetic non-smoker when compared with control subjects but this decrease in SNCV was statistically non-significant.

Decrease in sensory nerve conduction velocity in this study is consistent with study of Tupkovic E et al., which showed that sensory nerve conduction velocity was higher in control group as compared to diabetics [9]. But, in contrast to the present study Cerriza M et al., observed no deterioration of sensory nerve dysfunction in Type II diabetic patients [10]. This discrepancy in results is most likely due to the difference in patient selection and method of assessment.

In the current study more deterioration of nerve conduction velocity are found in nerves of lower limb as compared to upper limb. Kulkarni et al., also observed that nerves of lower limbs are more commonly affected as compared to upper limb suggesting that long nerves are more susceptible to diabetes assault [11].

The pathological mechanisms implicated in diabetic neuropathy, include microvascular damage [12], metabolic disorders [13], and changes in the interactions between neuronal and immunological systems along with glial cell activation [14]. When diabetic smokers were classified according to smoking index criteria, changes were observed in upper limb nerves of heavy smokers only. But in lower limb nerves both moderate and heavy smokers showed significant reduction in SNCV, however such changes were not seen in light smokers. Tayde MC et al., reported findings consistent with the present study [15]. Behse F et al., study also stated that there is usually a disproportionate and faster involvement of unmyelinated and small myelinated fibres than large nerve fibres [16].

In the later half of the study, it was found that for each increase in smoking index there was a significant decrease in SNCV of right median sensory nerve by (0.279 m/sec), left median sensory nerve (0.394m/sec), right ulnar sensory nerve (0.329 m/sec), left ulnar sensory nerve (0.334 m/sec), right sensory sural nerve (0.272 m/sec) and left sensory sural (0.293 m/sec). Smoking decreases blood supply to nerves and induces subclinical changes in myelin sheath leading to demyelination of nerves and a subsequent decrease in conduction velocity [17]. The demylinated axons have poor electrotonic conduction [18]. Also, it was found that heavy smokers have high carbon monoxide level which leads to hypoxia which is detrimental to peripheral nerves [19].

LIMITATION

As a result of time and fiscal constrain a small sample size was taken which reduces the statistical power of the study to a certain extent. Moreover, it could have given a better understanding of the underlying aetiology if reduction in SNCV of diabetic smokers would have been correlated with changes in nerve biopsy.

CONCLUSION

The results of present study suggest that apart from severity and duration of diabetes smoking itself is an independent risk factor for the development of diabetic neuropathy. Thus, the argument for its elimination is strengthened by the fact that both diabetes and cigarette smoking are individual risk factors for diabetic neuropathy and its diminution will probably cessate progression of neuropathy.

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