CHAPTER I

INVESTIGATION OF THE EFFECT OF CARDIOVASCULAR DISEASE RISK FACTORS ON NERVE CONDUCTION VELOCITIES.

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Neuropathy is general term which refers to nerve damage due to various conditions. Peripheral neuropathy is a common condition in which nerves of peripheral nervous system are affected. Patients usually complain of tingling, numbness, burning, pain, particularly in the hands and feet. Symptoms usually depend on type of the nerve involved (sensory, motor, and autonomic). Prevalence of peripheral neuropathy has been reported as 2.4% in general population (1). Its prevalence raises to 8% in diabetic patients (2, 3). Despite thorough diagnostic evaluation, the cause of neuropathy cannot be found in about 10-18% of cases (4, 5).

Most common causes of neuropathy are diabetes mellitus, trauma, infections, alcohol and toxins. Oxidative stress, vascular abnormalities and microangiopathy have been accused in etiology of diabetic neuropathy (6, 7). Hyperglycemia, age, smoking, hypertriglyceridemia and alcohol consumption are major independent risk factors for neuropathy in diabetic patients (8). It has been shown that irrespective of hypertension diagnosis, diabetic neuropathy is associated with elevated systolic blood pressure (9). Further, this association persists even if disease duration is relatively short (10). In a many clinical situations, there is an association between neuropathy and ischemia or hypoxia. Incidence of neuropathy is higher in patients with chronic obstructive pulmonary disease and peripheral arterial disease (11, 12). Thus, atherosclerotic risk factors may play role in pathogenesis of neuropathy.

The aim of the present study was to evaluate effect of atherosclerotic risk factors on nerve functions.

1. Material and Methods:

A total of 354 patient files were screened Between June – September 2020 and 74 subjects were enrolled in the study. Subjects with ischemic heart disease, congestive heart failure, hypo-hyperthyroidism, renal and/or hepatic disease, diabetes mellitus, B12 deficiency, paraneoplastic neuropathy were excluded from the study. Ethical committee approval was obtained from local ethics committee.

Demographic characteristics and biochemical values were recorded from patient's files. All biochemical analyses were done after a 12-hour fast. Blood samples were drawn from antecubital vein with the patient in an upright position.

Median and ulnar nerves were stimulated at the wrist and their sensory responses were recorded 13 and 11 cm from the stimulation point, respectively. Sural nerve (SN) was stimulated at a distance 14 cm from lateral malleolus and its sensory response was recorded from behind the lateral malleolus. Electrical stimulation of superficial peroneal nerve (PN) was performed 14 cm proximal to recording electrode; which was located on the dorsal aspect of the foot. In sensory nerve conduction study, distal latency, amplitude of sensory nerve action potential and conduction velocity was evaluated.

For the median motor nerve conduction study, recording electrode was placed on the muscle belly of abductor pollicis brevis, median nerve (MN) was stimulated at antecubital fossa 7 cm proximal to electrode and compound muscle action potentials (CMAP) were elicited. Motor nerve stimulation of the ulnar nerve (UN) was done at 7 cm proximal to the active recording electrode, above and below elbow. CMAP amplitudes from abductor digiti minimi were taken for analysis. Tibial nerve (TN) was stimulated behind medial malleolus 9 cm proximal to active electrode and in the popliteal fossa. CMAP amplitudes were recorded from abductor hallucis muscle. Deep peroneal nerve (PN) was stimulated at (1) the ankle, 9 cm proximal to the recording electrode, (2) the fibular head and (3) the popliteal fossa. CMAP amplitudes were recorded from extensor digitorum brevis muscle.

2. Statistical Methods

Scale parameters were described by means and standard deviations, nominal parameters were described with frequency analysis. Spearman's rho correlation analysis was used for correlations. SPSS 17.0 for windows was used for analysis at 95% confidence interval.

3. Results

74.0% of patients were female and 26.0% were male. Mean age of the subjects was 60.16±10.04. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 139.49±27.21 and 82.30±13.88 mmHg, respectively. 9.6% of subjects were smokers, and 4.8% were using alcohol. Clinical and demographic parameters of the subjects are shown in Table 1.

Sensory latency of median nerve (MN) was positively correlated with age, smoking, SBP and DBP, LDL-C, glucose levels ($p<0.05$). Glucose was the most affecting parameter. Sensory velocity of MN was negatively correlated with age, smoking, SBP, DBP, and LDL-C level ($p<0.05$).Sensory latency of ulnar nerve (UN) was positively correlated with glucose level. Sensory velocity of UN was negatively correlated with age. Sensory amplitude of sural nerve (SN) was negatively correlated with SBP and LDL-C level. The most affecting parameter was SBP. Sensory latency of peroneal nerve (PN) was positively associated with age, LDL-C, glucose levels. Glucose level was the most affecting parameter. Peroneal amplitude was negatively correlated with age and SBP ($p<0.05$). The most affecting factor was SBP. Peroneal velocity was negatively correlated with age and glucose level. Effect of glucose level on peroneal velocity was higher. Spearman's rho correlation analysis results for sensory parameters are given in Table 2.

Motor latency of MN was positively correlated with SBP, BMI and glucose level. SBP was the most affecting parameter. Motor latency of UN was positively correlated with age, SBP, DBP, LDL-C, AKS levels and BMI. SBP was the most affecting parameter. Motor velocity of UN was negatively correlated with age, SBP, glucose level and BMI. Motor latency of SN was positively correlated with SBP, glucose level, and BMI. Glucose was the most effective parameter. Motor amplitude of SN was negatively correlated with age and SBP ($p<0.05$). SBP was the most affecting parameter. Motor latency of PN was positively correlated with SBP, LDL-C, triglyceride and glucose levels, glucose level being the most effective factor. Peroneal velocity was negatively correlated with age, systolic pressure, LDL and glucose levels. Spearman's rho correlation analysis results for motor parameters are given in Table 3.

4.Discussion

In this study we aimed to evaluate peripheral nerve functions by using electrophysiological measurements and found that cardiovascular risk factors, such as age, smoking, BMI, high blood pressure, high triglyceride, LDL-C and glucose levels were associated with impaired peripheral nerve function. Among these risk factors, SBP and glucose level seemed to have prominent role.

Electrophysiological studies play key role for quantifying peripheral nerve function. Improvements in nerve conduction study techniques and computer software programs have enabled us to obtain more detailed information about nerve physiology. Results of nerve conduction studies are objective, repeatable, sensitive, specific and correlated with clinical neuropathy (13)

A lot of research has implicated the cardiovascular risk factors as a potential cause of peripheral neuropathy. Diabetes, prediabetes and obesity have been shown as the main metabolic components associated with peripheral neuropathy in a United States population (14). Although the pathophysiology of diabetic neuropathy is not well understood, impaired blood flow and oxygenation have been thought as important factors for it (15). Ischemia and hypoxia that occur due to diabetes related vascular and metabolic abnormalities may cause peripheral nerve damage and hence diabetic neuropathy (16). Several studies have shown that hypertension had a relationship with the occurrence of diabetic neuropathy (17-19). Forrest et al. found that the most important factor for the development of distal symmetrical diabetic neuropathy was hypertension (18). Another study reported that diabetic sensory peripheral neuropathy had an independent relationship with diabetes duration, weight, age, retinopathy, albuminuria, height, insulin use and hypertension duration (19). Diabetic neuropathy incidence has been linked to high triglyceride levels, BMI, smoking and hypertension (15). These studies showed that hypertension is a risk factor for diabetic neuropathy. Hypertension is associated with decreased pain perception and there are some evidence about the role of hypertension in pathogenesis of peripheral neuropathy (20-22). Hypertension may be an independent risk factor for chronic symmetrical neuropathy in older patients (21). Diabetic and non-diabetic hypertensives had higher sensory perception thresholds than controls (22). Edwards et al. found that untreated hypertensives had lower sensory action potential amplitudes despite normal peripheral nerve conduction velocities (23). Teunissen et al. investigated cardiovascular disease prevalence and risk factors in chronic idiopathic axonal neuropathy patients along with neuropathic findings in peripheral arterial disease patients. In their study, chronic idiopathic axonal neuropathy patients had more cardiovascular disease and risk factors, and peripheral arterial disease patients had more neuropathy events than control groups (24). Recently, studies performed on diabetic patients found that patients with hyperlipidemia have significantly higher incidence of peripheral neuropathy (25).

In our study cardiovascular risk factors, namely age, obesity, smoking, LDL-C, glucose and triglyceride levels, influenced the motor and sensory nerve function. We think that this relationship is related to atherosclerosis. Atherosclerosis is a systemic disease which can affect any part of the

vascular bed. Oxidative stress, inflammation, endothelial dysfunction, vascular lumen stenosis and microcirculatory disturbances result in possible ischemia in peripheral nerves.

Peripheral neuropathy is highly prevalent condition, especially in older subjects. Although it is not fatal, severe symptoms may lead to decreased quality of life for some patients. Therefore better understanding of underlying mechanisms and risk factors could be an important step for its prevention and the development of new treatment modalities.

Conflict of interest: None

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Table 1: Clinical and biochemical variables of the subjects.

Parameter	Value
Gender, n (%)	
Female	54 (74.0)
Male	19 (26.0)
Age, mean ± SD	60.16±10.04
Smoking, n (%)	7 (9.6)
Alcohol, n (%)	4 (6.8)
SBP	139.49±27.21
DBP	82.30±13.88
TC	200.58±33.63
LDL	131.88±29.62
HDL	47.66±9.71
VLDL	25.19±11.52
TG	109.41±51.04
Glucose	94.16±16.42
BMI	26.36±4.01

BMI: Body mass index, DBP: Diastolic blood pressure, HDL: High density level cholesterol, LDL: Low density level cholesterol, SBP: Systolic blood pressure, TC: Total cholesterol, TG: Triglyceride, VLDL: Very low density level cholesterol.

Table 2: Correlation analysis results of sensory parameters.

Sensory Parameters	Median			Ulnar			Sura			Per		
	LT	AMP	VEL	LT	AMP	VEL	LT	AMP	VEL	LT	AMP	VEL
Age	**,355****	-,027	**-,282***	,228	,014	**-,251***	,098	-,222	,013	**,371****	**-,233***	**-,252**
Smoking	**,256***	,096	**-,251***	,067	,135	-,138	-,041	-,137	-,106	,143	-,142	-,141
Alcohol	,188	-,046	-,095	,138	-,008	-,018	,068	,054	-,054	-,125	-,097	-,004
SBP	**,362****	-,130	**-,446****	,179	-,134	-,218	,132	**-,354****	-,127	,206	**-,251***	-,047
DBP	**,315****	-,051	**-,344****	,192	-,007	-,194	,028	-,193	-,056	,147	-,191	-,046
LDL	**,358****	-,128	**-,261***	,088	-,049	-,159	,171	**-,314****	-,186	**,295***	-,160	-,207
Glucose	**,517****	-,055	-,196	**,352****	-,044	-,211	,294*	-,075	-,080	**,383**	-,172	**-0,29**
BMI	,223	,073	-,042	,228	-,129	-,153	,243*	-,039	-,048	**,337***	-,097	-,107

*p<0.05, **p<0.01

BMI: Body mass index, DBP: Diastolic blood pressure, LDL: Low density level cholesterol, SBP: Systolic blood pressure.

Table 2: Correlation analysis results of motor parameters.

Motor parmeter	Median			Ulnar			Sura			Per		
	LT	**AMP**	**VEL**	**LT**	**AMP**	**VEL**	**LT**	**AMP**	**VEL**	**LT**	**AMP**	**VEL**
Age	,190	-,125	-,148	**,265***	-,125	**-,276***	,219	**-,298****	-,147	,188	,009	**-,319****
SBP	**,374****	,035	-,210	**,486****	,014	**-,306****	**,314****	**-,347***	-,150	**,240***	-,067	**-,286***
DBP	,205	,117	-,073	**,362****	,038	-,072	,157	-,210	-,095	,115	-,067	-,182
LDL	,226	-,013	-,160	**,283***	-,009	-,087	,208	-,126	-,115	**,234***	,160	**-,410****
TG	0,23	-,138	-,162	,225	,003	-,110	0,2	-,071	-,072	**,239***	-,088	-0,16
Glucose	**,336****	-,075	-,188	**,318****	-,198	**-,241***	**,372****	-,059	-,167	**,389****	-,042	**-,238***
BMI	**,253***	,103	,074	**,307****	-,109	**-,269***	**,275***	-,216	-,023	,128	,114	-,170

*p<0.05, **p<0.01

BMI: Body mass index, DBP: Diastolic blood pressure, LDL: Low density level cholesterol, SBP: Systolic blood pressure, TG: Triglyceride.