International Journal of Research and Review
Vol. 9; Issue: 3; March 2022
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

A Comparative Study of Sensory and Motor Peripheral Nerve Functions in Elderly Patients of Diabetes Mellitus and Non-Diabetic Controls in a Tertiary Care Hospital

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DOI: https://doi.org/10.52403/ijrr.20220339

ABSTRACT

Introduction: In elderly diabetics, peripheral neuropathy is a significant cause of morbidity and physical disability. Diabetes Mellitus, and its chronic complications like peripheral neuropathy have been instrumental in contributing to the physical decline in the elderly. However, objective assessment of physical ability in elderly diabetics and devising their correlation to reduced peripheral nerve functions has been a hitherto uncharted territory. This study aims at evaluating the peripheral nerve functions in elderly diabetics. This study hypothesizes that peripheral nerve functions were significantly reduced in elderly diabetics in comparison to elderly nondiabetics.

Materials and Method: Relevant history, prescriptions and laboratory reports were collected from the study participants. Sensory functions were tested by 10g Semmes-Weinstein Monofilament Test and Vibration Perception Threshold (VPT) was tested by handheld biothesiometer. Motor functions were tested by the Compound Muscle Action Potential and Nerve Conduction Velocity (CMAP and NCV respectively) for the peroneal nerve (preferably of right side). Fisher exact test has been applied barring the parameters for nerve function with respect to Monofilament and VPT. For Monofilament and VPT, Z statistic has been used to test the differences in proportion.

Results: Most of the diabetic patients were overweight. NCV and CMAP were significantly reduced in diabetics. Mean NCV in diabetic group was 37.81 m/s as compared to 42.08 in non-diabetic. Mean CMAP in diabetics was 2.55 mV as compared to 3.21 mV in non-diabetic. Our study showed that number of participants with impaired VPT and monofilament test was higher in diabetics than non-diabetics.

Conclusion: Diabetic patients are more prone to develop peripheral neuropathy. Assessment of the clinical homologue of these pathological processes is the first step in implementing the appropriate type of intervention. Treatment should be individualized to take into account specific manifestations and the underlying pathogenesis of each patient's unique clinical presentation.

Keywords: Diabetes Mellitus, Nerve Function, Peripheral Neuropathy.

INTRODUCTION

The World Health Organisation's (WHO) holistic definition of health as a state of complete physical, mental and social well-being has been widely accepted as being more appropriate, when ascribed to older people, than the application of a narrower biomedical model of health which concentrated on the pathological state and

the resulting physical and psychological condition. [1] When we talk of older persons, the attention is focused towards aging which is a progressive, generalized impairment of function resulting in loss of adaptive response to stress and increasing risk of age-related diseases and disabilities. The overall effect of these alterations is, increase in the probability of suffering from disabilities and dying, which is evident from rising age-specific death rates in the population. It is this association with suffering from disabilities and death that makes aging frightening. Aging occurs at various levels: molecular, cellular, physiological, morphological, chronological, social, and behavioural. Biologists interested in the problem of aging are studying genetic, molecular, biochemical, biophysical, structural and physiological changes occurring in various animals after the attainment of reproductive maturity. [2]

As modern management of disease has improved with greater understanding of the disease process, so also the number of people beyond the age of 60 years has increased. It is documented that the number of people above the age of 60 years has increased from 56 million in 1991 to more than 70 million in the year 2001. [3]

Type 2 Diabetes Mellitus (T2DM) is a classical example of aging disease process and with increasing life expectancy, T2DM in elderly is one of the most important challenging contemporary issues. The aging process is characterized by the progressive constriction of the homeostatic reserve of every organ system. This decline is commonly defined as homeostenosis and is being highlighted from the evolving evidences and its frequency is increasing.[4] One of the inevitable consequences is the impairment in glucose homoeostasis. Diabetes mellitus is widely prevalent in the elderly population all over the world. As predicted by the WHO, India will have largest number of diabetic patients in the world and the increase in the number of diabetic populations will be more in the age group of 60 and above. The characteristics of the geriatric population impose certain important consideration in the epidemiology, pathophysiology, diagnosis and treatment of those afflicted with diabetes. Along with the increase in the diabetics in this age group, the greatest challenge to the medical profession would be to take care of the complications associated with disease itself. Also, the economic consequences of this morbid illness are staggering.

The rising trend of diabetes in the elderly and questions regarding treatment options -basic care vis-a-vis aggressive care have prompted a lot of research. Many studies have been undertaken to address the problems in the management of diabetes in this special group, which is at increased risk because of both the effect of ageing on the existing disease-Type 1 or Type 2 Diabetes, as well as the subset of geriatric onset diabetes. This needs to be considered to draw relevant conclusions on effective counter-measures. Possible mechanisms associated with age related impairment in glucose uptake by muscle include: a) Decreased muscle mass, b) increasing obesity, c) decreased physical activities, d) poor diet, e) increased plasma free fatty acid levels.

Probability of diabetic complications like neuropathy, nephropathy, retinopathy is higher in elderly patients. Sixty four percent of elderly diabetics studied in JIPMER, Pondicherry had retinopathy while diabetic nephropathy was reported by 66% of participants. [3] Fifty two percent had neuropathy while 56% had evidence of autonomic neuropathy. Coronary heart disease was detected in 26%. Infections were present in almost 60% of elderly diabetics. One patient had hyperosmolar coma whereas 16% had documented ketoacidosis. In 1997, two-thirds of all costs for diabetes in the US were borne by elderly people. Attributable indirect costs totalled $ 54.1 billion. Total direct costs were estimated at $ 77.7 billion

Peripheral neuropathy is one of the most disabling complications of diabetes in

the elderly and the prevalence is estimated to be around 50%. [5-7] In elderly diabetics, peripheral neuropathy is a significant cause of morbidity and physical disability.

There are many biological changes that keep on progressing throughout the aging process that can lead to pathophysiology of diabetic neuropathy. These include an increase in the production of advanced glycosylated end-products, an impairment in the polyol pathway, changes in nerve and vessels and impaired response to oxidative stress. Due to difficulty in clinical diagnosis of clinical presentation of peripheral neuropathy characterised by age-related changes in the peripheral and autonomic nervous system, diagnosis is often based on nerve conduction studies, vibration perception threshold determination and autonomic function tests. [8]

The decline of physical performance in the elderly has long been trivialized as a natural corollary of the aging process. However, the complex interrelationship between aging, disease and physical disability lies far deeper than what meets the eye. Focused research activities in recent years have attempted to unearth objective measures for physical performance in the elderly. [9] There has also been an increased attempt to correlate the objective decline in physical performance with the underlying disease process.

Diabetes Mellitus, and its chronic complications like peripheral neuropathy have been instrumental in contributing to the physical decline in the elderly. However, objective assessment of physical ability in elderly diabetics and devising their correlation to reduced peripheral nerve functions has been a hitherto uncharted territory. This study aims at evaluating the peripheral nerve functions in elderly diabetics. This study hypothesizes that peripheral nerve functions were significantly reduced in elderly diabetics in comparison to elderly nondiabetics.

MATERIALS & METHODS

This research was an observational, cross-sectional & comparative hospital-based study, conducted at department of endocrinology and general medicine, SKMCH, Muzaffarpur, Bihar, India. The study was started after permission from Institutional Ethics Committee and after taking voluntary informed consent from the study participants. The study duration was twenty-four months from November 2017 to October 2019.

The study was carried out in 120 elderly individuals aged 60 years and above. They were divided into 2 groups:

Group 1 (Test Arm): Comprising of 60 patients who had Type 2 Diabetes Mellitus.

Group 2 (Control Arm): Comprising of 60 subjects who did not have Diabetes Mellitus (control group). The controls were selected from the relatives of the patients attending the Outdoor as well as relatives of those admitted at the hospital SKMCH, Muzaffarpur.

Both groups were matched for age & sex.

Inclusion Criteria (Group 1 – Test Arm):

1. Age > 60 years
2. Patients with diagnosis of type 2 Diabetes Mellitus as per WHO and ADA (2017) criteria[10]
3. No difficulty in performing activities of daily life, climbing stairs and walking at least a quarter of a mile

Inclusion Criteria (Group 2 – Control Arm):

1. Elderly subjects aged > 60 years.
2. Non-diabetic elderly subjects
3. No difficulty in performing activities of daily life, climbing stairs and walking at least quarter of a mile.

Exclusion Criteria:

1. Age < 60 years
2. Type 1 Diabetes Mellitus
3. Patients with history of intake of drugs causing peripheral neuropathy like phenytoin, isoniazid, vincristine and others.

4. Patients with history of CVA, hip and knee osteoarthritis, fracture of hip or any other such conditions that restrict lower extremity mobility in elderly.
5. Patients with history of life-threatening cancers with no active treatment during last 3 years.
6. Peripheral neuropathy due to causes other than Diabetes Mellitus.
7. Evidence of cardiac disease as per history, clinical examination and ECG.
8. Patients on high dose metformin (1.5gm / day & above) therapy.
9. Malnourished subjects with concomitant hypovitaminosis.
10. H/O alcohol addiction in the present or recent past (3 years).

Relevant history, prescriptions and laboratory reports were collected from the study participants. Sensory functions were tested by 10g Semmes-Weinstein Monofilament Test[11] and Vibration Perception Threshold (VPT)[12] was tested by handheld biothesiometer. Motor functions were tested by the Compound Muscle Action Potential and Nerve Conduction Velocity (CMAP and NCV respectively)[13] for the peroneal nerve (preferably of right side).

Statistical Analysis:

Based on the sample size of sixty for each group, chosen randomly from the diabetic patients (cases) and the non diabetic controls respectively, the different parameters for the peripheral nerve functions were observed and recorded. To analyse the differences, Fisher exact test has been applied barring the parameters for nerve function with respect to Monofilament and VPT as they were measured in terms of non numerical value. For Monofilament and VPT, Z statistic has been used to test the differences in proportion of normal cases between diabetic and non diabetic subjects. All the data were analysed using SPSS statistical software.

OBSERVATIONS & RESULT

Table 1: Baseline Demographic Variables

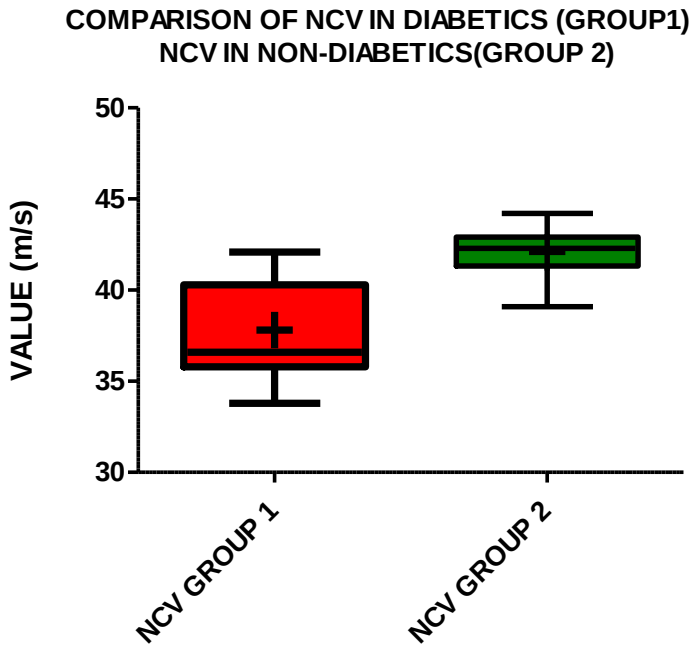
Parameters	Group 1 (Diabetic) n = 60	Group 2 (Non-Diabetic) n = 60	P -Value	Remarks
	Mean ± Std. Deviation	Mean ± Std. Deviation		
Age (Years)	70.08 ± 4.82	70.12 ± 4.99	0.97	NS
Sex Male Female	 41 19	 39 21		
Height (cm)	170.38 ± 5.64	171.27 ± 3.93	0.32	NS
BMI (kg/m2)	26.08 ± 2.02	24.36 ± 0.71	0.38	NS
Creatinine (mg/dl)	1.2 ± 0.35	1.06 ± 0.24	0.009	S
Hypertension (%)	61.6	56.7	0.58	NS
Dyslipidaemia (%)	60	56.6	0.91	NS
Current Smoker (%)	12	15	0.86	NS

Analysis of results using Fisher exact test to find the differences between diabetic and non diabetic groups with respect to NCV are as follows:

Table 2. Comparison of NCV in Diabetics (Group 1) and Non-Diabetics (Group 2):

Mean NCV value in diabetics (m/s)	Mean NCV values in non-diabetics (m/s)	Calculated value of Fisher test	Table value of Fisher test with 118 d.f. at significance level of 5%	Table value of Fisher test with 118 d.f. at 1% level of significance	Two-tailed "p" value	Inference
37.81	42.08	4.75	1.64	2.33	<0.0001	Significant

Our data showed mean NCV in diabetics to be significantly reduced than that in non-diabetics ($p<0.0001$).



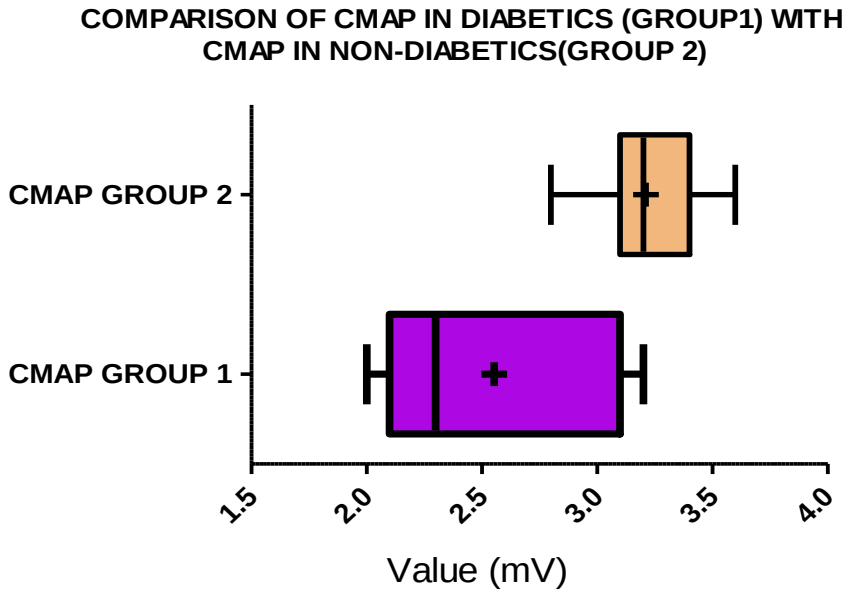
Box-plot showing comparative analysis of NCV in diabetics (group 1) and NCV in non-diabetics (group 2)

Analysis of results using Fisher exact test to find the differences between diabetic and non diabetic groups with respect to CMAP are as follows:

Table 3: Comparison of CMAP in Diabetics (Group 1) and Non- Diabetics (Group 2):

Mean CMAP value in diabetics(mV)	Mean CMAP value in non-diabetics(mV)	Calculated value of Fisher test	Observed value of Fisher test with 118 d.f. at significance level of 5%	Observed value of Fisher test with 118 d.f. at 1% level of significance	Two-tailed "p" value	Inference
2.55	3.21	9.75	1.64	2.33	<0.0001	Significant

Our data showed mean CMAP in diabetics to be significantly reduced than that in non-diabetics ($p < 0.0001$).



Box-plot showing comparative analysis of CMAP in diabetics (group 1) and non-diabetics (group 2)

Analysis of VPT done by Z statistic to test the differences in proportion of normal cases between diabetic and non diabetic groups show:

Table 4: Comparison of VPT in Diabetics (Group 1) and Non- Diabetics (Group 2):

Proportion of normal VPT in diabetics	Proportion of normal VPT in non-diabetics	Proportion of impaired VPT in diabetics	Proportion of impaired VPT in non-diabetics	Calculated value of Z	Table value of Z	Two-tailed "p" value
24 out of 60	44 out of 60	36 out of 60	16 out of 60	2.00	1.96	0.04

Our data shows VPT in diabetics to be significantly impaired than VPT in non-diabetics ($p<0.05$).

Analysis of Monofilament Test done by Z statistic to test the differences in proportion of normal cases between diabetic and non diabetic groups show:

Table 5: Comparison of Monofilament Test in Diabetics (Group 1) and Non- Diabetics (Group 2):

Proportion of normal Monofilament in diabetics	Proportion of normal Monofilament in non-diabetics	Proportion of impaired Monofilament in diabetics	Proportion of impaired Monofilament in non-diabetics	Calculated value of Z	Table value of Z	Two-tailed "p" value
26 out of 60	43 out of 60	34 out of 60	17 out of 60	3.33	1.96	0.0009

Our data shows Monofilament test in diabetics to be significantly impaired than that in non-diabetics ($p<0.001$).

DISCUSSION

This study was a hospital-based cross-sectional comparative study to evaluate various parameters of peripheral nerve functions in elderly diabetics. Both the groups were similar in respect of age of participants and there was no statistically significant difference. The two groups have a similar sex distribution. The seemingly greater number of males could be explained by the fact that women often neglect their initial symptoms and seek medical advice late due to personal and family pressure. Thus, in a hospital-based study, women patients form a minority.

Most of the diabetic patients were overweight. This observation is corroborated by studies showing the prevalence of high BMI in Indian population with type 2 Diabetes Mellitus. [14] serum creatinine, though within the normal limits, were higher in the diabetic population. This could be explained by the greater incidence of nephropathy in the diabetic population. [15]

There were more participants with hypertension and dyslipidaemia in diabetic group than non-diabetic group. But these differences were not found to be statistically significant. This finding can be justified by the evidences supporting the fact that hypertension and dyslipidaemia are commonly associated with diabetes. Moreover, the presence of other chronic complications of diabetes like nephropathy and peripheral vascular disease may contribute to the development of hypertension. These data corroborate with existing literature on the prevalence of Hypertension, Dyslipidaemia, Nephropathy and Retinopathy in Type2 Diabetes Mellitus. [16]

The variations in sensory and motor peripheral nerve functions were studied in the diabetic group and in the non-diabetic group. NCV and CMAP of the peroneal nerve was studied for assessing motor functions and VPT and 10g S-W Monofilament test were utilized for evaluating sensory functions. [13] The peroneal nerve, rather than the sural nerve, was selected because it is a motor nerve and more likely to have a response in older adults. [17]

NCV and CMAP were significantly reduced in diabetics. These findings corroborate with those of Strotmeyer S, Reikeneire N [18] et al who found NCV (P< 0.001) and CMAP (p<0.05) of the peroneal nerve to be significantly reduced in an elderly U.S. population in comparison with elderly non-diabetics. KB Stansberry, HE Resnick et al [19] evaluated 39 adults, aged 70-79 years and had similar results in the diabetic population.

Our study showed that number of participants with impaired VPT and monofilament test was higher in diabetics than non-diabetics. These differences were also found to be statistically significant. Our study results parallel the findings of various studies conducted worldwide. KB Stansberry, HE Resnick et al [19] in their study on 39 elderly subjects found that diabetic subjects had significantly impaired pressure sensation than non-diabetic controls (P < 0.05), and significantly impaired VPT (p < 0.05). Strotmeyer S, Reikeneire N et al [18] et al in their ground-breaking analyses for the Health, Aging, and Body Composition (Health ABC) Study participants showed significant impairment of VPT (p< 0.001) and Monofilament Test (p< 0.001).

Thus, in diabetics, parameters of sensory and motor peripheral nerve functions (NCV, CMAP, VPT and Monofilament test) were significantly reduced than that in the non-diabetics.

The term diabetic neuropathy (DN) comprises of a wide range of nerve impairment and are quite common, with different prevalence rates reported from various studies depending on the different diagnostic criteria. [20-22] Diabetic neuropathies impair both the peripheral and autonomic nervous system and cause serious illness and death in both Type 1 and Type 2 diabetes patients. Diabetic neuropathy is the most common type of neuropathy, causing hospitalization above all other complications of diabetes combined, and is responsible for 50-75% non-traumatic amputation. [23,24] In geriatric patients with diabetes, peripheral neuropathies are problematic mainly due to their harmful effects on stability, sensorimotor function, mobility, and daily lifestyle. [25-27] In the U.S from 1999-2000, 28% of adults aged 70-79 and 35% of adults aged ≥80 years experienced peripheral neuropathy based on a simple screening of reduction in foot sensation. [28]

CONCLUSION

Diabetic patients are more prone to develop peripheral neuropathy. Assessment of the clinical homologue of these pathological processes is the first step in implementing the appropriate type of intervention. Treatment should be individualized to take into account specific manifestations and the underlying pathogenesis of each patient's unique clinical presentation. In older patients, special care should be taken to manage pain while improving daily functioning and mobility, with very few side effects from pharmacotherapy. Older patients are at greater risk for falls and fractures due to neuropathy, weakness and need strength exercise and physiotherapy. Ultimately agents that deal with high fibre abnormalities will be needed if there is need to halt the pathophysiology of impairment in QOL and ADL due to neuropathy in old diabetic patients.

ACKNOWLEDGEMENT

We are thankful to the healthcare workers (faculty members) of IGIMS, Patna for their support.

Conflict of Interest: None

Source of Funding: None
Ethical Approval: Approved

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How to cite this article: Kumar D, Kumari R, Bano S et.al. A comparative study of sensory and motor peripheral nerve functions in elderly patients of diabetes mellitus and non-diabetic controls in a Tertiary Care Hospital. *International Journal of Research and Review*. 2022; 9(3): 343-351. DOI: *https://doi.org/10.52403/ijrr.20220339*

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