Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 08, 2022

Original research article

Study of autonomic nervous dysfunction in patients of diabetes mellitus and its relations with the duration of disease

[1]Dr. Meena Arora, [2]Dr. Rajiv Arora, [3]Dr. Parminder Singh, [4]Dr. Gagan Khanna

[1]Associate Professor, Department of Physiology, Punjab Institute of Medical Sciences, Jalandhar, Punjab, India

[2]Professor, Department of Physiology, Punjab Institute of Medical Sciences, Jalandhar, Punjab, India

[3]Associate Professor, Department of Medicine, Sri Guru Ram Das Institute of Medical Sciences & Research, Sri Amritsar, Punjab, India

[4]Professor, Department of Orthopedics, Sri Guru Ram Das Institute of Medical Sciences & Research, Sri Amritsar, Punjab, India

Corresponding Author:

Dr. Meena Arora (meenakhanna2013@gmail.com)

Abstract

Background: Diabetes is most common amongst the endocrine and metabolic disorders. It is chronic disorder of carbohydrate, fat and protein metabolism attributed to either diminished production of insulin or resistance to its actions.

Diabetes is known to produce microvascular and macrovascular changes in the body leading to various complications like diabetic nephropathy and diabetic retinopathy. Involvement of nervous system (neuropathy) is also a well-established complication in diabetic patients. Amongst the neuropathies associated with diabetes, involvement of autonomic nervous system has been found by many researchers.

Aim: Our study is aimed at finding relationship of autonomic neuropathy with the duration of the disease in diabetes.

The present study was conducted on 100 patients in 4 different groups depending upon duration of disease i.e. Group I, II, III and IV have duration of disease <2 years, 2-5 years, 5-10 and >10 years respectively. The examination of autonomic nervous system has been carried out with Heart rate, respiratory rate, pulse, temperature and area of excessive sweating or anhidrosis.

Conclusion: This study revealed that the neuropathy was directly proportionate to the duration of disease. Parasympathetic activity also showed a gradual deterioration starting earlier in the disease course but progressing, similar to the sympathetic neuropathy with the duration of disease.

Keywords: Autonomic, diabetes, nephropathy, parasympathetic, sympathetic

Introduction

Diabetes is the most common amongst the endocrine and metabolic disorders. Diabetes mellitus is a chronic disorder of carbohydrate, fat and protein metabolism attributed to diminished production of insulin or resistance to its actions. The deficiency of insulin either absolute or relative evolves from interaction between genetic and environmental factors. Diabetes is characterized by chronic hyperglycemia of defined degree with or without glucosuria, hyperlipidemia or tendency to develop ketoacidosis [1]. Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes, often overlooked and misdiagnosed. It is a systemic-wide disorder that may be asymptomatic in the early stages. After a long duration of metabolic derangements specific complications of diabetes like retinopathy, nephropathy and neuropathy may occur [2].

The diagnosis of autonomic neuropathy relies mainly on detecting its cardiovascular component, particularly abnormalities in heart rate control and response of blood pressure to postural changes. Loss of heart rate variability is the hallmark of CAN and is diagnosed by measuring heart rate response to physiological stimuli [3].

Langley divided the autonomic outflow into parasympathetic and sympathetic components based on their special origin as well as differential effects of nerve stimulation on various tissues [4]. Cannon proposed that parasympathetic efferent mediate more precise, target focused responses than did sympathetic which have more wide spread effect. The ability of parasympathetic ganglion cells to provide selective regulation of various autonomic functions is due to general anatomic arrangement in which parasympathetic ganglion cells are located within or near the innervated tissue.

In autonomic nervous system many organs are doubly innervated, receiving fibres from both sympathetic and parasympathetic divisions. Parasympathetic nerve fibres regulate resting type functions e.g.

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 08, 2022

emptying of urinary bladder whereas sympathetic responses are involved in the body's preparation for physical activity e.g. strenuous muscular work [5].

The autonomic neuropathies are a group of disorders in which small fibres both myelinated and unmyelinated fibres are selectively involved. In developed countries the most common cause of autonomic neuropathy is diabetes [6].

Diabetic autonomic neuropathy may affect up to 30% of the patients, although, most of the patients have only mild or subclinical features. An overt clinical syndrome develop slowly and is quite rare despite a high frequency of functional abnormalities. The incidence of this clinical syndrome may be seen in up to 5% [3].

The present study is therefore designed to investigate autonomic nervous system involvement in the patients of diabetes mellitus in term of duration of desease.

Aims and Objectives: Aim of the study is to assess the autonomic nervous system activity in the patients of diabetes having different disease duration and to compare the changes in autonomic nervous system activity in different group of diabetic people with varying disease duration.

Material and Methods: The present study has been conducted on hundred patients of diabetes mellitus type II. The autonomic nervous system is divided into sympathetic nervous system and parasympathetic nervous system. In the present study activity of both wings of ANS (autonomic nervous system) will be assessed in the patient of diabetes mellitus type II having different disease duration. The patients were divided into 4 groups depending on the duration of disease. Each group comprise of 25 patients. Group I has <2 years, Group II has 2-5 years, Group III has 5-10 years and Group IV has >10 years of disease duration.

The examination of autonomic nervous system has been carried out with Heart rate, respiratory rate, pulse, temperature and area of excessive sweating or anhidrosis.

Autonomic function tests: The various autonomic function tests were carried out with the help of Cardiart-108T/MK-VI ECG machine (BPL make) using standard limb lead II. But for Galvanic Skin Resistance Polyrite-4 Medicare Machine was used. Polyrite recorder is a highly sensitive oscillograph capable of simultaneously recording signals in different modes from many sources. The various autonomic function tests were carried out. The sympathetic activity was measured by cold pressor test, handgrip test and galvanic skin resistance test while parasympathetic activity was measured by S/L ratio, 30:15 ratio, valsalva ratio and tachycardia ratio using ECG machine.

Results

This study was carried out on hundred patients presented in medicine OPD having diabetes from few years. After statistical analysis we observed that the mean values of pulse rate showed a significant rise in mean pulse rate in group II (82.80±9.99) compared to group I (81.68±8.11) (p<0.05), group III (90.36±11.58) compared to group I (81.68±8.11) (p<0.05) and group IV (80.88±13.94), compared to group III (90.36±11.50) (p<0.05). However, there was no statistical significant change in mean pulse rate in the group II when compared to group I and group IV when compared to group I and group II (p>0.05). (Table I)

Table I: Pre-Test Mean Values of Pulse Rate and Blood Pressure in the Four Groups (n = 100)

Parameter	Group I	Group II	Group III	Group IV
Pulse rate (per min)	81.68±8.11	82.80±9.99	90.36±11.58	80.88±13.94
SBP (mmHg)	136.48±13.90	145.84±7.57	143.04±6.83	140.24±12.27
DBP (mmHg)	77.28±8.90	88.00±7.02	83.84±7.61	82.24±7.99

Parameter	p-value					
	II v/s I	III v/s I	IV v/s I	III v/s II	IV v/s II	IV v/s III
Pulse rate (per min)	>0.05^{NS}	<0.05^{S}	>0.05^{NS}	<0.05^{S}	>0.05^{NS}	<0.05^{S}
SBP (mm Hg)	<0.05^{S}	<0.05^{S}	>0.05^{NS}	>0.05^{NS}	>0.05^{NS}	>0.05^{NS}
DBP (mm Hg)	<0.05^{S}	<0.05^{S}	<0.05^{S}	<0.05^{S}	<0.05^{S}	>0.05^{NS}

Data presented as Mean ± SD; SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

The mean changes in systolic blood pressure showed a statistical change in the group II and group III when compared to group I (p<0.05) as shown in Table II. Similarly, there were statistical significant changes in mean diastolic blood pressure in group II, group III and group IV when compared to group I (p<0.05). Group III and group IV when compared to group II (p<0.05). However, there was statistically insignificant variation in mean diastolic blood pressure in the group III and group IV (p>0.05). These changes in mean values in group IV, group III and group II compared to group I as well as group IV and

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 08, 2022

group III compared to group II and group II as compared to group I are indicative of some deterioration of parasympathetic as well as sympathetic activity. These findings are consistent with the findings of the study in which there was early rise of parasympathetic neuropathy up to 10 years followed by concurrent involvement of sympathetic nervous system [7].

Table II: Comparative Study of Sympathetic Functions in Four Groups (N = 100)

Parameter	Group I	Group II	Group III	Group IV
CPT				
Rise in SBP (mm Hg)	16±2.24	14.4±2.38	13.28±1.90	12±1.29
Rise in DBP (mm Hg)	16.8±2.24	15.84±2.94	13.12±3.47	14.80±4.40
HGT				
Rise in SBP (mm Hg)	17.76±2.47	16.56±1.96	16.32±2.36	16.8±2.89
Rise in DBP (mm Hg)	18.64±2.43	16.24±3.38	14.72±3.65	13.04±3.27
GSR (Kohm)	160±5.42	166.04±8.69	168±9.24	172±8.86

Data presented as Mean ± SD; CPT: Cold pressor test; HGT: Hand grip test; GSR: Galvanic skin resistance; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Parameter	p-value					
	II v/s I	III v/s I	IV v/s I	III v/s II	IV v/s II	IV v/s III
CPT						
Rise in SBP (mm Hg)	$<0.05^{S}$	$<0.05^{S}$	$<0.05^{S}$	$>0.05^{NS}$	$<0.05^{S}$	$<0.05^{S}$
Rise in DBP (mm Hg)	$>0.05^{NS}$	$<0.05^{S}$	$<0.05^{S}$	$<0.05^{S}$	$>0.05^{NS}$	$>0.05^{NS}$
HGT						
Rise in SBP (mm Hg)	$>0.05^{NS}$	$<0.05^{S}$	$>0.05^{NS}$	$>0.05^{NS}$	$>0.05^{NS}$	$>0.05^{NS}$
Rise in DBP (mm Hg)	$<0.05^{S}$	$<0.05^{S}$	$<0.05^{S}$	$>0.05^{NS}$	$<0.05^{S}$	$>0.05^{NS}$
GSR (Kohm)	$<0.05^{S}$	$<0.05^{S}$	$<0.05^{S}$	$>0.05^{NS}$	$<0.05^{S}$	$>0.05^{NS}$

NS: Not significant; S: Significant

Table III shows a comparison of the mean values of rise in systolic and diastolic blood pressure in all the four groups in response to cold pressor test and handgrip test. Table III also shows changes in mean value of GSR from group I to group IV. Table III shows a significant increase in systolic blood pressure in patients of group IV, group III and group II when compared to group I (p<0.05), group IV when compared to group III and group II (p<0.05). But there is statistically insignificant change in the group III patients compared to group II.

Table III: Comparative Study of Parasympathetic Function Tests in Four Groups (n = 100)

Parameter	Group I	Group II	Group III	Group IV
S/L ratio	1.18±0.08	1.12±0.09	1.02±0.02	0.99±0.06
30:15 ratio	1.05±0.09	1.01±0.04	1.00±0.05	0.98±0.08
Valsalva ratio	1.6±0.29	1.52±0.34	1.40±0.35	1.36±0.33
Tachycardia ratio	0.81±0.07	0.80±0.09	0.76±0.07	0.75±0.08

Data presented as Mean ± SD; SL: Standing to lying ratio

Parameter	p-value					
	II v/s I	III v/s I	IV v/s I	III v/s II	IV v/s II	IV v/s III
S/L ratio	$<0.05^{S}$	$<0.05^{S}$	$<0.05^{S}$	$<0.05^{S}$	$<0.05^{S}$	$<0.05^{S}$
30:15 ratio	$>0.05^{NS}$	$<0.05^{S}$	$<0.05^{S}$	$>0.05^{NS}$	$>0.05^{NS}$	$>0.05^{NS}$
Valsalva ratio	$>0.05^{NS}$	$<0.05^{S}$	$<0.05^{S}$	$>0.05^{NS}$	$>0.05^{NS}$	$>0.05^{NS}$
Tachycardia ratio	$>0.05^{NS}$	$<0.05^{S}$	$<0.05^{S}$	$>0.05^{NS}$	$>0.05^{NS}$	$>0.05^{NS}$

There is statistically less increase in systolic blood pressure from group I to group IV indicating the involvement of sympathetic nervous system from group I to group II probably due to some damage to the nervous system. The changes in diastolic blood pressure also shows statistically significant decreased rise from group I to group III indicating a progressive decline in sympathetic activity from group I to group IV. These findings of the present study are consistent with a study that showed that lower diastolic cold pressor results in patients with sympathetic dysfunction [8].

Table III also shows variation in systolic blood pressure and diastolic blood pressure in all the four groups in response to hand grip test. The variations in systolic blood pressure from group I to group IV was statistically insignificant (p>0.05). However, statistically significant changes in diastolic blood pressure were observed in patients of group IV when compared to group I and group II (p<0.05) but insignificant change when compared to group III (p>0.05). There was less increase in diastolic blood pressure in the group IV (13.04$\pm$3.27) compared to 18.64$\pm$ 2.43 in group I (p<0.05), and 16.24$\pm$3.38 in the group II (p<0.05). There was significantly less increase in systolic blood pressure variation in group

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 08, 2022

III (14.72±3.65) when compared to group I (18.64±2.43 (p<0.05). However, there was no significant change in the group III when compared to group II.

The result of hand grip test to changes in systolic blood pressure and diastolic blood pressure are similar to the study which showed significant abnormal hand grip test in diabetic patient with longer duration of disease [9].

Table III shows a progressive increase in the Galvanic skin resistance (GSR) mean values from 160±5.42 in group I to 166±8.69 in group II, 168±9.24 in group III and 172±8.82 in group IV patients.

There is statistically significant increase in GSR in patients of group IV, III and II when compared to group I (p<0.05) and group IV when compared to group II (p<0.05) indicating a progressive decline in sympathetic sufficiency.

Table III shows the variation in S/L ratio, 30:15 ratio, Valsalva ratio and tachycardia ratio from Group I to Group IV. The simple test to assess the cardiac parasympathetic activity is the heart rate response to the lying down (S/L ratio). Statistical comparison of S/L ratio showed significant variation in its mean value when compared between group IV (0.99±0.06), group III (1.02±0.02), group II (1.12±0.09) and group I (1.18± 0.08) (p<0.05).

This observation is favorably compared with the results of the study showing lower values of the S/L ratio in patients with diabetic autonomic neuropathy (1.07±0.04) as compared to normal young subjects (1.25±0.15) [10]. The 30:15 ratio test shows a statistically significant change from group I (1.05±0.09) to group III (1.00 ±0.05) and group IV (0.98 ±0.08) (p<0.05).

The result is in accordance with the study conducted on 22 normal and 25 diabetic patients which showed 15 diabetic patients have 30:15 ratio <1.03 and 10 patients had <1.00 ratio [55].

Parasympathetic function tests also included stress inducing test like Valsalva maneuver. Table IV shows the changes in Valsalva ratio from group I to group IV. There is statistically significant change in group IV (1.36±0.33) and group III (1.40±0.35) compared to group I (1.60±0.29) (p<0.05). However, Group IV and III showed statistically insignificant variation when compared to group II (p>0.05).

These changes in Valsalva ratio are consistent with the earlier findings conducted on 76 subjects with diabetic duration <10 years duration which showed that the progression of autonomic neuropathy is monitored best longitudinally by the valsalva ratio. This ratio is important in monitoring the deterioration of autonomic function tests with the passage of time [11].

Tachycardia ratio as shown by Table III also shows, statistically significant changes in the group IV (0.75±0.08) and group III (0.76±0.07) when compared to group I (0.81±0.07) (p<0.05).

Discussion

The results of the present study are in agreement to a study conducted on 20 diabetic patients in which 70% showed abnormal sympathetic skin response [12]. Thus, blood pressure response to CPT and hand grip test as well as changes in GSR from group I to group IV are indicative of a progressive deterioration of sympathetic function i.e. diabetic sympathetic neuropathy. The sympathetic dysfunction is more in diabetic duration of 5-10 years and more [13].

Correlating together the findings of S/L ratio, 30:15 ratio, Valsalva ratio and tachycardia ratio there is increased parasympathetic dysfunction with the duration of disease. This is in agreement with the study conducted on 133 patients who were examined at the baseline and after 5 years and 10 years of follow up which showed the increase in frequency of parasympathetic neuropathy at 5 years and 10 years follow up [14, 15, 16, 17].

The present study is also in agreement with the study that showed significant association between diabetic autonomic neuropathy and prolonged duration of diabetes [18, 19].

The present study has further confirmed that the earlier findings of different workers that the duration of the disease has direct bearing on the deteriorating autonomic nervous system function in diabetic patients (Type II).

Conclusions

The present study was conducted to find any changes in the autonomic nervous system activity in diabetic patients with varying duration of disease. An in-depth analysis of autonomic nervous system activity was measured with the help of various tests conforming sympathetic as well as parasympathetic activity in both the sexes of all age groups in type 2 diabetes mellitus.

The response to various sympathetic function tests showed a gradual deterioration in the sympathetic activity called diabetic sympathetic neuropathy. The sympathetic neuropathy was more prominent in diabetic cases with the duration of 5-10 years and more than 10 years. Thus, the neuropathy was directly proportionate to the duration of disease.

On the other hand, parasympathetic activity also showed a gradual deterioration starting earlier in the disease course but progressing, similar to the sympathetic neuropathy with the duration of disease. Thus, the duration of diabetes directly involves the autonomic nervous system activity leading to autonomic neuropathy.

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 08, 2022

Reference

1. Siddharth NS, Tripathy BB. Diabetes mellitus, A.P.I Textbook of Medicine, 5th Edition, 1992, 211-236.
2. Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kabayashi M. Report of committee on classification and diagnostic criteria of diabetes mellitus. Diab Res Clin Proact. 2002 Jan;55(1):65-85.
3. Nabil Aly, Philip Weston. Autonomic neuropathy in older people with diabetes mellitus. (Clinical) J Diabetes Nurs. 2002;6(1):10.
4. Shaun F. Morrison. Differential control of sympathetic outflow. Am J Physiology Regul. Integr. Comp Physiol. 2001;281:683-693.
5. Autonomic neuropathy [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases. NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases, 2022. [cited 2022 Nov 21]. Available from: https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/nerve-damage-diabetic-neuropathies/autonomic-neuropathy
6. Freman R. Autonomic peripheral neuropathy. Lancet. 2008;365(9466):1259-70.
7. Spallone1 V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis and management. Diabetes Metab Res Rev. 2011;27:639-53.
8. Bashir M, Lone RA, Salroo IN, Sayeed SI. Assessment of vascular reactivity in young diabetics by cold pressor test and heart rate variability. Med J DY Patil Vidyapeeth. 2019;12:11-5.
9. Dafaalla MD, Nimir MN, Mohammed MI, *et al*. Risk factors of diabetic cardiac autonomic neuropathy in patients with type 1 diabetes mellitus: a meta-analysis. Open Heart 2016;3:e000-336. Doi: 10.1136/openhrt-2015- 000336
10. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J Diabetes Investig. 2013 Jan;4(1):4-18.
11. Low PA, Tomalia VA, Park KJ. Autonomic function tests: some clinical applications. J Clin Neurol. 2013 Jan;9(1):1-8.
12. Nazhel B, Yetkin I, Irkec C, Kocer B. Sympathetic skin response in diabetic neuropathy. Electromyogr Clin Neurophysiol. 2002;42(3):181-85.
13. Toyry JP, Nishkanen LK, Mantysaari MJ, Lansimies EA, Unsitupa MI. Occurrence, predictors and clinical significance of autonomic neuropathy in NIDDM. Ten year follow up from the diagnosis. Diabetes. 1996;45(3):308-15.
14. Valensi P, Huard JP, Giroux C, Attali JR. Factors involved in cardiac autonomic neuropathy in diabetic patients. J Diabetes Complications. 1997;11(3):180-87.
15. Levitt NS, Stansberry KB, Wynchank S, Vinik AI. The natural progression of autonomic neuropathy and autonomic function tests in a cohort of people with IDDM. Diabetes Care. 1996;19(7):751-54.
16. Balcıoğlu AS, Müderrisoğlu H. Diabetes and cardiac autonomic neuropathy: Clinical manifestations, cardiovascular consequences, diagnosis and treatment. World J Diabetes. 2015 Feb;6(1):80-91.
17. Ewing DJ, Campbell IW, Murray A, Neilson JMM, Clarke BF. Immediate heart rate response to standing: simple test for autonomic neuropathy in diabetes. Br Med J. 1978;1:145-47.
18. Ahmed AM, Hussein A, Ahmed NH. Diabetic autonomic neuropathy. Saudi Med J. 2000;21(11):1034-37.
19. Verrotti A, Prezioso G, Scattoni R, Chiarelli F. Autonomic neuropathy in diabetes mellitus. Front Endocrinol (Lausanne). 2014 Dec;5:205.