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Assessment of Autonomic Function Using the Isometric Handgrip Test and Heart-Rate Changes During the Valsalva Manoeuvre in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study in Northeast India

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Abstract
Background: *Diabetic autonomic neuropathy is an often-under-recognised complication of diabetes mellitus. Cardiovascular autonomic function can be assessed using non-invasive bedside tests, including the isometric handgrip test and the Valsalva manoeuvre. This study assessed autonomic responses in adults with type 2 diabetes mellitus (T2DM) and examined their relationship with diabetes duration and HbA1c.*
Materials and Methods: *A hospital-based cross-sectional observational study was conducted in the Department of Physiology, Agartala Government Medical College and GBP Hospital, Agartala. Fifty adults with T2DM were included in the reported analysis. The Valsalva ratio and change in diastolic blood pressure (ΔDBP) during handgrip at 30% of maximum voluntary contraction for one minute were assessed. A Valsalva ratio ≥1.20 and a ΔDBP >15 mmHg was considered normal, as specified in the study protocol.*
Results: *The mean age was 53.46 ± 7.91 years and mean BMI was 22.69 ± 2.45 kg/m². Mean diabetes duration was 7.54 ± 2.22 years and mean HbA1c was 7.92 ± 1.06%. Mean Valsalva ratio was 0.972 ± 0.202 and mean ΔDBP was 9.04 ± 4.34 mmHg. An abnormal Valsalva ratio was observed in 37 (74%) participants and an abnormal handgrip DBP response in 28 (56%). At least one test was abnormal in 40 (80%). Mean diabetes duration was 8.33 ± 1.70 years in the group classified as having autonomic dysfunction and 4.40 ± 0.84 years in the group without it ($p<0.001$). Diabetes duration was inversely correlated with Valsalva ratio (Spearman $\rho=-0.823$; $p<0.001$). The association between HbA1c and Valsalva ratio was negative but not statistically significant.*
Conclusion: *Autonomic dysfunction is very common in people with Type 2 diabetes mellitus and longer the duration of diabetes higher the occurrence of autonomic dysfunction. Isometric hand grip test and valsalva menoveour are simple bedside test to assess the autonomic dysfunction which can be used routinely for screening in people with type2 DM.*
Keywords: *Type 2 diabetes mellitus; diabetic autonomic neuropathy; cardiovascular autonomic neuropathy; Valsalva manoeuvre; isometric handgrip test; HbA1c.*

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I. INTRODUCTION

Diabetes Mellitus is a complex metabolic disorder characterized by increased blood sugar level. It affects multiple systems of our body due to its microvascular and macrovascular complications. In developing countries like India diabetes poses a major health care burden because of the disease course and its related complications. Cardiovascular complications are very common and one of the major causes of mortality in diabetics.

Diabetic autonomic neuropathy (DAN) is a less recognized complication despite of its significant impact on mortality and morbidity of the diabetic patients. The prevalence of DAN increases with the duration of diabetes. It may be identified in patients at the time of diagnosis of DM in up to 7 percent but can be as high as 50 percent after 15 years. It can be manifested by dysfunction of cardiovascular, gastrointestinal, genitourinary, sudomotor system. Cardiac autonomic neuropathy can manifest as resting tachycardia, exercise intolerance, orthostatic hypotension, and impaired neurovascular function etc[1].

Cardiovascular manifestation of DAN is one of the life-threatening complications. Cardiovascular autonomic neuropathy leads to hampered life of patients because of postural hypotension, unawareness of

hypoglycemic symptoms, exercise intolerance, chronic fatigue, and increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction[2].

Several hypotheses had been suggested to explain the pathogenesis of DAN. The metabolic alteration in diabetes, generation of advanced glycosylation end products can lead to widespread inflammation of autonomic nerves. Neurovascular insufficiency as a result of activation of protein kinase C mediated vasoconstriction in diabetics also can cause neuronal damage. Increased oxidative stress, with increased free radical production, causes vascular endothelium damage and reduces nitric oxide bioavailability leading to neurovascular insufficiency. Reduction in neurotrophic growth factors, deficiency of essential fatty acids also results in altered nerve function. Damage to the autonomic nerves is manifested by dysfunction in various organ systems[2,3].

Various autonomic function tests are available which are noninvasive and easy to perform. One of the tests is isometric hand grip test which involves assessment of blood pressure changes following isometric hand grip. There should be a rise in diastolic blood pressure during isometric pressing of a handgrip dynamometer at approximately one third of the maximum contraction strength for 1 min[4]. Another test for assessing autonomic function is evaluation of heart rate changes during Valsalva manoeuver[5]. Various studies have been done to assess the autonomic function in DM using isometric hand grip test and Valsalva maneuver[6,7].

Various studies were done in different parts of India to assess the autonomic function in type 2 diabetics. But numbers of studies done in Northeastern part of India are very few. This part of India is geographically and ethnically different. Also, because of the difference in food habits, life style and cultural values the disease manifestations might vary. Therefore, this study is taken up to evaluate the autonomic function in type 2 diabetic people using isometric hand grip test and heart rate changes during Valsalva maneuver.

II. METHODOLOGY

Study type: Observational Study
Study design: Hospital based Cross- sectional study
Study area/Location: Department of Physiology in collaboration with Department of Medicine, Agartala Govt. Medical College (AGMC), Agartala.
Study Population: 50Adults with type 2 Diabetes Mellitus attending Diabetes and Nutritional Clinic of AGMC & GBP Hospital, Agartala

Inclusion criteria:
1. Diagnosed cases of Type 2 Diabetes Mellitus as given by the American Diabetes Association (ADA)[27]
Patients who fulfill the following criteria for the diagnosis of diabetes mellitus:
a. Symptoms of diabetes plus random blood glucose (RBS) concentration ≥ 11.1 mmol/l (200 mg/dl) or
b. Fasting plasma glucose (FBS) ≥7.0 mmol/l (126 mg/dl) or
c. Hemoglobin A1c ≥ 6.5% or
d. 2-hour plasma glucose (PPBS) ≥ 11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test.
2. Patients having no cardiovascular complaints.
3. Co-operative and willing to participate in the study.

Exclusion criteria:
1. Subjects who did not give consent.
2. Patients who are hypertensive, suffering from renal failure
3. History of disease that can cause autonomic neuropathy like alcoholic neuropathy, multiple system atrophy, thyroid disorders.
4. History of taking any drug that can cause neuropathy or affect Autonomic function tests like beta blockers
5. Subjects who have addiction like nicotine, alcohol.

Study tools:
- Electrocardiograph (Model No. CARDIART 6108T) available in the department of Physiology, AGMC and GBP Hospital.
- Hand grip dynamometer
- Sphygmomanometer- Mercury Deluxe BP apparatus (diamond allied products)
- Stethoscope
- Height measuring stand- Bioplus; height 200cm
- Weighing machine - Victoria Dx
- Case study format

Data collection:
Data was collected from the participants (selected as elaborated in the sub-heading sampling procedure) only after obtaining their informed consent as per the inclusion criteria. Socio-demographic variables like name, age, sex, etc. were noted as per the case study format. The duration of Type 2 Diabetes Mellitus and their Blood Sugar (RBS, FBS, PPBS) and HbA1c levels was noted from their medical documents.
A pre-designed case study format was used to collect relevant information, demographic data, medical history and clinical features for each patient using a standard questionnaire.
Isometric hand grip test: After obtaining informed consent the subject was asked to apply pressure on a standardized handgrip dynamometer at a maximum voluntary contraction. There after 30% of this maximum value was asked to sustain for a period of 1 minute. The blood pressure was measured before and at 1-minute intervals during the handgrip. The result was expressed as the difference between the highest diastolic pressure during the handgrip and the diastolic pressure at rest before the handgrip. A rise of diastolic BP more than 15 mmHg during the handgrip was considered normal.
Valsalva maneuver: The subject was asked to exhale forcefully through a mouth piece which was attached to a manometer to generate a pressure of 40 mmHg and this level is maintained for 15 sec. During this maneuver, and 45 seconds subsequent to this, the ECG is recorded and the Valsalva ratio is calculated, which is the ratio between the maximal R-R interval (after the release of the strain) and the minimal R-R interval (during the strain). A ratio of 1.20 or more was considered as normal.
Data analysis: Data was entered in computer using Microsoft Excel. Descriptive statistics and other suitable statistical tests like χ^2 test, Independent Sample t-test, etc. was used as per applicability. A probability value less than 0.05 was considered as significant.

III. RESULT

A total of 50 patients with Type 2 Diabetes Mellitus participated in the study. The mean age of the study participants was **53.46 ± 7.91 years** and mean BMI was **22.69 ± 2.45 kg/m²** as shown in table 1.

Table 1. Demographic Profile and Anthropometric measures of the study participants

Variables	Mean ± SD
Age (years)	53.46 ± 7.91
Weight (Kg)	57.40 ± 6.8034
Height (meters)	1.5984 ± 0.106
BMI (kg/m²)	22.69 ± 2.45

The mean duration of diabetes was 7.54 ± 2.22 years, while the mean HbA1c was 7.92 ± 1.06% as shown in table 2.

Table 2. Distribution of Duration of Type 2 Diabetes Mellitus and HbA1C level among study participants

Variables	Mean ± SD
Duration of Type 2 Diabetes Mellitus	7.54 ± 2.22
HbA1c (%)	7.92 ± 1.06

The mean Valsalva ratio was 0.972 ± 0.202, and the mean rise in diastolic blood pressure during exercise was 9.04 ± 4.34 mmHg among the study participants as shown in table 3

Table 3. Valsalva Ratio and Rise of Diastolic Blood pressure among study participants.

Variables	Mean ± SD
Valsalva ratio	**0.972 ± 0.202**
Rise in DBP during exercise (mmHg)	**9.04 ± 4.34**

An abnormal Valsalva ratio was observed in 37 patients (74%), while an abnormal diastolic blood pressure response was observed in 28 patients (56%) as shown in table 4.

Table 4. The proportion of autonomic neuropathy among study participants with Type 2 Diabetes Mellitus

Autonomic parameter	Abnormal	Normal
Valsalva ratio	37 (74%)	13(26%)
Diastolic BP rise	28 (56%)	22 (44%)
Either test	40 (80%)	10 (20%)

The duration of diabetes was substantially higher among patients with autonomic neuropathy. The mean duration of diabetes among patients with autonomic neuropathy was 8.33 ± 1.70 years, compared with 4.40 ± 0.84 years among those without autonomic neuropathy as shown in table 5. This difference was statistically significant ($p < 0.001$)

Table 5. Duration of diabetes and autonomic neuropathy

Group	n	Duration of diabetes, mean ± SD
Autonomic neuropathy present	40	8.33 ± 1.70 years
Autonomic neuropathy absent	10	4.40 ± 0.84 years

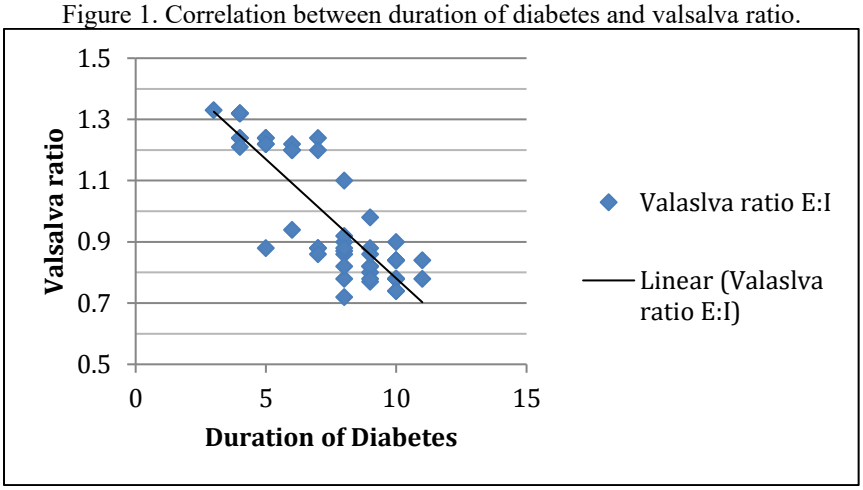
Occurrence of autonomic neuropathy among the participants according to the duration of diabetes is shown in table 6.

Table 6. Autonomic Neuropathy (AN) and duration of diabetes

Duration of diabetes	AN absent n (%)	AN present: n (%)	Total
≤5 years	9 (75.0%)	3 (25.0%)	12
6–10 years	1 (2.8%)	35 (97.2%)	36
>10 years	0 (0%)	2 (100%)	2
Total	10	40	50

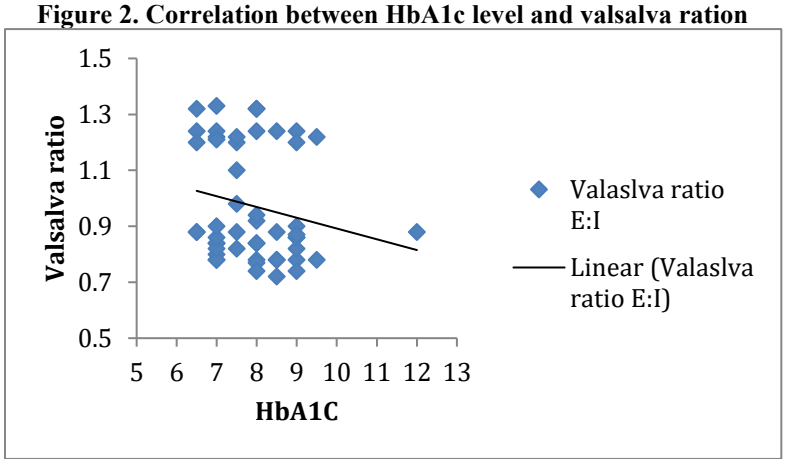
There was inverse correlation between duration of diabetes and Valsalva ratio (**$\rho = -0.823$, $p < 0.001$**) provides evidence that prolonged exposure to diabetes is associated with deterioration in cardiovascular autonomic function as shown in figure 1

Figure 1. Correlation between duration of diabetes and valsalva ratio.



There was also a negative correlation between HbA1C level and valsalva ratio but was not significant as shown in figure 2.

Figure 2. Correlation between HbA1c level and valsalva ration



IV. Discussion

Current study found a substantial inverse relationship between diabetes duration and Valsalva ratio, showing that cardiovascular autonomic function declines with diabetes duration. Similar results were observed in the study conducted by Vinik et al., 2003; Verrotti et al., 2014[2-3]. A moderate negative connection was identified between diabetes duration and ΔDBP during the isometric hand-grip test, indicating impairment of sympathetic cardiovascular responses with increasing duration of diabetes. Study conducted by Zygmunt and Stanczyk, 2010; Makwana et al., 2012 showed similar result[4,6]. These findings are consistent with the progressive nature of diabetic autonomic neuropathy, which involves metabolic, vascular, oxidative, and microvascular factors that influence autonomic nerve function as concluded by Greene et al., 1988; Cameron and Cotter, 1997; [12,14].

HbA1c had modest and non-significant negative relationships with Valsalva ratio and ΔDBP, indicating that it may not accurately represent established cardiovascular autonomic dysfunction (Kempler et al., 2020; Siddiqui et al., 2023). Overall, the findings highlight the significance of diabetes duration in cardiovascular autonomic.

Overall, the findings highlight the significance of diabetes duration in cardiovascular autonomic dysfunction and back up the therapeutic value of bedside autonomic function testing (Assessment, 1996; Makwana et al., 2012)[5,6].

The relationship between HbA1c and autonomic function in the present study was relatively weak and statistically non-significant. This observation suggests that a single measurement of HbA1c may not adequately reflect the extent of established cardiovascular autonomic dysfunction. Although chronic hyperglycemia plays an important role in the development of diabetic neuropathy, autonomic nerve damage may also be influenced by the cumulative duration of metabolic disturbances, age, hypertension, dyslipidemia and other associated risk factors. Moreover, HbA1c reflects glycemic control over a relatively short period and may not represent the cumulative glycemic exposure responsible for long-term neuronal injury. Nevertheless, the absence of a

significant association in the present study should not be interpreted as evidence that glycemic control has no role in autonomic neuropathy.[28]

An important finding of the present study is the potential clinical usefulness of simple bedside autonomic function tests. The Valsalva man oeuvre and isometric hand-grip test are non-invasive physiological tests that provide information about cardiovascular autonomic reflexes. These tests can help identify subclinical autonomic abnormalities that may not be apparent during routine clinical examination. Their use may be particularly relevant in resource-limited clinical settings, where sophisticated autonomic testing facilities are not always available.[29]

Vinik et al. (2013) emphasized that cardiovascular autonomic neuropathy is an important complication of diabetes, characterized by impaired sympathetic and parasympathetic regulation, altered sympathovagal balance and increased cardiovascular risk. They described parasympathetic dysfunction as an early manifestation of CAN and highlighted the importance of the Valsalva man oeuvre and other bedside cardiovascular autonomic reflex tests for its detection.[30]

V. CONCLUSION

The study demonstrates a strong inverse correlation between the duration of type 2 diabetes and cardiovascular autonomic function, specifically noted through the Valsalva ratio and changes in diastolic blood pressure (ΔDBP) during isometric hand-grip tests. The findings suggest that autonomic responses are progressively impaired as diabetes duration extends, indicating that diabetes duration may be a more crucial predictor of autonomic dysfunction than HbA1c levels. Regular screening using basic bedside tests like the Valsalva maneuver could aid in the early detection of autonomic dysfunction in type 2 diabetes patients.

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