Section: General Medicine

Original Research Article

A STUDY ON THE ASSOCIATION OF CARDIAC AUTONOMIC NEUROPATHY WITH SILENT MYOCARDIAL ISCHEMIA

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ABSTRACT

Background: Patients with diabetes mellitus have a 2-4 times higher risk of coronary artery disease (CAD) than those without. Women with diabetes lose cardiovascular protection traditionally associated with their gender, and asymptomatic ischemic heart disease (IHD) is common in this population. The association between cardiac autonomic neuropathy (CAN) and silent myocardial ischemia warrants further investigation. This study aimed to determine the prevalence of asymptomatic IHD in women with diabetes using the treadmill test (TMT) and evaluate the correlation between CAN and asymptomatic IHD. **Materials and Methods:** This cross-sectional observational study was conducted in a tertiary college hospital. Among the 107 diabetic women screened, 30 met the inclusion criteria and underwent TMT and CAN assessment. TMT positivity, defined as inducible ischemia without angina or CAN, was evaluated using standardized bedside tests. **Results:** The prevalence of TMT-positivity was 30%. CAN positivity was significantly higher in the TMT-positive group (77.78%) than in the TMT-negative group (10.52%) ($p<0.001$). TMT-positive patients exhibited significantly lower exercise capacity, as reflected by the reduced exercise duration ($p=0.016$) and greater autonomic abnormalities, including reduced heart rate variation to deep breathing ($p=0.0027$), reduced heart rate increase after standing ($p=0.0026$), and greater systolic blood pressure drop after standing ($p<0.001$). The TMT-positive group's heart rate variability during deep breathing was significantly lower (11.67 ± 7.45 vs. 20.16 ± 5.41, $p=0.0027$), showing impaired parasympathetic activity. **Conclusion:** The prevalence of asymptomatic IHD in women with diabetes was substantial, with one-third of the participants showing positive TMT results. CAN is strongly associated with TMT positivity, indicating its potential role in silent myocardial ischemia.

INTRODUCTION

Patients with diabetes have a 2-4-fold increased risk of CAD.[1,2] Better implementation of therapies that reduce cardiovascular risk in patients with diabetes will require moving beyond the primary focus on glycemic control. Working knowledge of the effects of diabetes mellitus on the heart and blood vessels will aid physicians in caring for these patients. In the general population, women experience relative protection from myocardial infarction and usually develop CAD approximately 10 years later than men do. However, diabetes blunts the cardiovascular benefits of female sex.[3]

In the first National Health and Nutrition Examination Survey (NHANES) and the NHANES epidemiologic follow-up survey conducted 10 years apart, age-adjusted mortality decreased in non-diabetic men and women but less so in diabetic men and increased by 23% in diabetic women.4 In the Gruppo Italiano per 10 studio della sopravvivenza bell Infarto miocardio - 2 (GISSI-2) study of thrombolytic therapy in patients with myocardial infarction, diabetes increased the death rate by 40% in men and 90% in women.[5]

In the Finnish contribution to the WHO Multinational Monitoring of Trends and Determinants of Cardiovascular Disease, 1-year mortality was 38% higher in diabetic men and 86% higher in diabetic women.[6] Silent myocardial ischemia, which is common in patients with diabetes, can be detected using the treadmill test. In developing nations such as

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India, the cost-effective treadmill test can be used as an investigation modality for diagnosing CAD in high-risk populations such as diabetic women.[7]

Diabetic autonomic neuropathy is the most common and troublesome complication of type 2 Diabetes mellitus.[8] Cardiovascular autonomic neuropathy is a common form of autonomic neuropathy that causes abnormalities in heart rate control and central and peripheral vascular dynamics. Cardiac autonomic neuropathy has been linked to postural hypotension, exercise tolerance, enhanced intraoperative cardiovascular lability, increased incidence of asymptomatic ischemia, myocardial infarction, and a decreased likelihood of survival after myocardial infarction.[9] Hypotheses concerning the multiple etiologies of diabetic neuropathy include metabolic insult to nerve fibers, neurovascular insufficiency, autoimmune damage, and neurohumoral growth factor deficiency.[8] Cardiac autonomic neuropathy, which is considered to be a cause of asymptomatic CAD in patients with diabetes, is tested by history and simple bedside tests. Its presence is correlated with silent myocardial ischemia.

Aim

This study aimed to correlate the presence of cardiac autonomic neuropathy with asymptomatic ischemic heart disease.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in a tertiary college hospital. The study population consisted of 107 women with diabetes attending the outpatient clinic, of whom 30 were selected based on specific inclusion criteria.

Inclusion Criteria

Known diabetic women on treatment (OHA and insulin therapy), diabetic women not on treatment for CAD, patients not on the beta-blocker duration of diabetes within 10 years, and those with normal echocardiography were included.

Exclusion Criteria

Patients with peripheral vascular disease, type 1 diabetes mellitus, known CAD, signs of left ventricular failure, uncontrolled systemic hypertension, high-risk unstable angina, age >65 years, and other absolute contraindications for exercise stress testing.

Method

The presence of cardiac autonomic neuropathy (CAN) was assessed through history taking and simple bedside tests in the selected group. The correlation between CAN and asymptomatic ischemic heart disease was evaluated. Asymptomatic ischemic heart disease was defined as positive inducible ischemia during the treadmill test without angina at rest. Fasting plasma glucose levels were measured using the glucose oxidase and pyruvate oxidase methods from overnight fasting samples, whereas postprandial blood sugar was assessed two hours after breakfast.

Body Mass Index (BMI) was calculated using the following formula: BMI= Weight kg/height m2. The patients were categorized into three groups based on their BMI: < 25, 25–30, and > 30. Treadmill test (TMT) positivity was analyzed in these groups.

Several tests have been performed to assess cardiac autonomic neuropathy. These included measuring the heart rate response to deep breathing (defined as six breaths per minute), heart rate increases 15 s after standing using an ECG monitor, and a drop in systolic blood pressure two minutes after standing. A positive diagnosis of CAN required a heart rate variation to deep breathing of < 10 beats/min, an increase of < 12 beats/min after standing, and a drop in systolic blood pressure of > 20 mmHg.

The treadmill test used the standard Bruce protocol because of its extensive diagnostic and prognostic data. Patients were instructed to refrain from eating or consuming caffeinated beverages for three hours before testing and to wear comfortable clothing. Adequate skin preparation was performed to ensure high-quality recordings. Heart rate, blood pressure, and electrocardiography (ECG) findings were recorded during each exercise stage and recovery.

Statistical Analysis

Statistical analysis was performed on the data collected from 30 patients using Microsoft Excel 2003 and SPSS version 13.0. Variables such as age, duration of diabetes, BMI, systemic hypertension, menopausal status, and CAN positivity in both TMT TMT-positive and TMT-negative groups were analysed. The significance of the differences in means was calculated using z-tests for means and chi-squared tests for proportions, with statistical significance set at ($p < 0.05$).

RESULTS

The study population was divided into TMT-positive and TMT-negative groups. They were matched for age, BMI, mean duration of diabetes, percentage of CAN positivity, systemic hypertension, and menopause. No statistical difference was noted between the two groups in terms of age, BMI, mean duration of diabetes, systemic hypertension, and menopause. In all the parameters compared between these two groups, the ‘p’ value is >0.05, which is statistically insignificant. But for cardiac autonomic neuropathy between these two groups, the ‘p’ value is <0.001. This value was statistically significant and strongly associated with cardiac autonomic neuropathy in the TMT-positive group. [Table 1]

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Table 1: Comparison of clinical and demographic characteristics between TMT positive and TMT negative groups

	TMT Positive Group	TMT Negative Group	P value
Number	9	19	-
Age	49.78±8.11	45.21±7.66	0.16
BMI	27.39±3.91	27.01±4.10	0.84
Mean duration of diabetes	5.78±3.31	4.32±2.81	0.27
% of autonomic neuropathy positivity	77.78%	10.52%	<0.001
SHT	55.55%	42.10%	0.48
Menopause	22.22%	15.78%	0.69

TMT parameters like exercise duration in minutes, % of target heart rate and work done in METs are compared between TMT positive and TMT negative groups. Exercise performed in minutes was significantly different between the two groups (p=0.016). This indicates poor exercise capacity in the TMT-positive group.

While comparing both groups for heart rate variation to deep breathing, heart rate increased 15 sec after standing and dropped in SBP 2 min after standing, the 'p' values are 0.0027, 0.0026, and <0.001. This showed a strong association with cardiac autonomic neuropathy in the TMT-positive group. [Table 2]

Table 2: Comparison of exercise and autonomic parameters between TMT positive and TMT negative groups

	TMT positive	TMT negative	P value
Exercise time	5.51±1.91	7.43±2.19	0.016
Workload in METs	8.81±2.28	10.59±2.71	0.06
% Predicted maximum HR	91.5±9.71	90.71±10.14	0.12
HR variation to deep breathing	11.67±7.45	20.16±5.41	0.0027
HR increases 15 seconds after standing	12.22±3.90	16.47±2.65	0.0026
Drop in SBP 2 min After standing	20.67±7.42	8.95±6.01	<0.001

DISCUSSION

In our study, the mean age of the TMT-positive group (49.78±8.11) was greater than that of the TMT-negative group (45.21±7.66), similar to the study by Lavekar et al. The mean age of subjects in the TMT positive group (53.56±7.41 years) was significantly higher than that of the TMT negative group (48.71±8.72 yrs).10 Our mean BMI in the TMT-positive group was 27.39±3.91, similar to the study by Handargal et al., who reported that, among 162 patients, TMT was positive in 63 (38.9%) study subjects with a BMI of 29.69±3.58.[11] Lavekar et al. reported that 34 out of 161 patients (21.1%) were positive for exercise-induced ischemia.[10]

In our study, where female patients with diabetes were the target population, TMT positivity was slightly lower (30%). Cardiac autonomic neuropathy in 77.78% of TMT-positive patients, cardiac autonomic neuropathy was positive in seven TMT-positive cases. This shows a strong relationship between cardiac autonomic neuropathy and silent myocardial ischemia. Similar to a study by Gupta et al., the prevalence of TMT positivity and autonomic neuropathy in treadmill-positive patients was 38% and 72.2%.[12]

In our study, a significant difference in exercise duration was observed between the TMT-positive (5.51±1.91 min) and TMT-negative groups (7.43±2.19 min, p=0.016). Similar to the study by Christman et al., shorter exercise duration in patients with positive TMT results in diminished exercise tolerance among these individuals. The reduced exercise capacity in the TMT-positive group leads to underlying ischemic heart disease, which limits the ability to sustain physical exertion.[13]

In our study, the workload achieved in METs was lower in the TMT-positive group (8.81±2.28) than in the TMT-negative group (10.59±2.71), although this difference was not statistically significant (p=0.06). Similar to the studies done by Handargal et al., Gupta et al., Sharma et al., Radhika et al. All these studies reported that the workload achieved in METs was lower in the TMT-positive group compared to the TMT-negative group, though this difference was not statistically significant.[11,14,15,16]

In our study, the percentage of predicted maximum heart rate achieved during exercise was similar between the two groups (91.5±9.71% in TMT-positive vs. 90.71±10.14% in TMT-negative, p=0.12), similar to study by Verity and Ismail, results regular exercise can improve cardiovascular disease risk factors in postmenopausal women with non-insulin-dependent diabetes mellitus, including increased maximum oxygen uptake and maintenance of high-density lipoprotein levels.[17] The study by Huebschmann et al. reports that women with type 2 diabetes perceive exercise as more difficult than non-diabetic women, which may be a barrier to physical activity.[18] The study by Colberg et al. reports heart rate reserve (HRR) and rating of perceived exertion (RPE) remain valid methods for prescribing and monitoring exercise intensity in diabetic women, even those with autonomic neuropathy.[19] Yadav and Gunjal reported diabetic women show delayed heart rate recovery after exercise, which is associated with an increased risk of cardiovascular disease.[20]

In our study, the TMT-positive group's heart rate variability during deep breathing was significantly lower (11.67±7.45 vs. 20.16±5.41, p=0.0027), showing impaired parasympathetic activity. The increase in heart rate 15 seconds after standing was significantly lower in the TMT-positive group

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(12.22±3.90 vs. 16.47±2.65, p=0.0026). Studies by Rasmussen et al., Bennett et al., and Katayama et al. reported a significant lowering of HRV in T2DM patients compared to healthy controls.[21,22,23]

Limitations and recommendations

Our study sample size of 30 patients may limit the generalizability of our findings. As a cross-sectional design, this study captures associations at a single point in time, making it challenging to establish causality. The lack of longitudinal follow-up restricts the assessment of CAN changes over time. Potential confounding factors, such as medication use and lifestyle choices, were not controlled for, and the focus on female patients may limit applicability to broader demographics.

Future research should involve larger and more diverse populations to validate these findings and to explore the mechanisms linking CAN with asymptomatic IHD. Longitudinal studies are needed to establish causal relationships and assess the impact of interventions targeting CAN on reducing silent ischemia risk. Clinicians should adopt a comprehensive approach involving regular screening for CAN and incorporating cardiovascular risk assessments into routine care. Increased awareness among healthcare providers and patients regarding the implications of CAN in cardiovascular health is crucial. Future studies should investigate targeted interventions aimed at improving cardiac autonomic function and their potential impact on reducing asymptomatic IHD incidence in diabetic patients.

CONCLUSION

The prevalence of asymptomatic ischemic heart disease was higher in women with diabetes than in those without. The prevalence of cardiac autonomic neuropathy was higher in treadmill-positive patients who were otherwise asymptomatic. This showed a significant association between silent myocardial ischemia and cardiac autonomic neuropathy in the diabetic population. Poor exercise capacity was noted in women with TMT-positive, but otherwise asymptomatic diabetes.

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