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Assessment of Cardiac Autonomic Neuropathy in Patients with Diabetes Mellitus: A Tertiary Care Hospital Study

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ABSTRACT

Background

Atherosclerotic coronary artery disease, diabetic cardiomyopathy, and cardiac autonomic neuropathy (CAN) are the three categories into which the cardiovascular consequences of diabetes can be grouped. After all other potential causes have been ruled out, cardiovascular autonomic neuropathy—often referred to as CAN in the literature—is defined as the impairment of autonomic regulation of the cardiovascular system. Finding people with CAN is crucial because, if detected early enough, comprehensive therapies focusing on lifestyle, glucose management, and cardiovascular risk factors can reverse the course of CAN and delay its progression. In order to better understand CAN in individuals with diabetes mellitus (DM) and how it relates to risk factors, the current study was conducted.

Materials and methods

Sixty consecutive diabetic patients were selected to be included in our study, diagnosed as per the American Diabetes Association (ADA). The presence of CAN was assessed with the help of Ewing's Battery, composed of five bedside tests.

Observations

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Out of 60 patients, a total of 53 patients (88.3%) with DM had CAN. Of these, 38.3% showed early CAN, 38.3% showed definite CAN, and 7% showed severe CAN. The abnormal E:I (exhalation/inhalation) ratio, noticed in 75% of patients, was the most frequently observed abnormal autonomic function test that tests the parasympathetic nervous system. The ECG's QTc interval prolongation provides good specificity for diagnosing CAN as well as assessing its severity, but the majority of cases showed low sensitivity.

Conclusion

Since CAN has a significant association with mortality, every patient diagnosed with DM should be evaluated for CAN at the time of diagnosis as well as on an annual basis thereafter, as recommended by the ADA. Optimal glycemic management and lifestyle modification at the initial stages of diabetes may prevent CAN-related complications.

Keywords: CAN, Diabetes,

Introduction

Between 1980 and 2000, the percentage of adults over 18 who had diabetes increased from 4.7 to 8.5% worldwide.1 With 8.7% of people in India between the ages of 20 and 70 having diabetes, the disease is becoming increasingly problematic.2 India is thought to be the diabetes capital of the globe. Three categories can be used to categorize diabetes-related cardiovascular complications: diabetic cardiomyopathy, atherosclerotic coronary artery disease, and cardiac autonomic neuropathy (CAN).3

The impairment of autonomic regulation of the cardiovascular system, after other causes have been ruled out, is known as CAN. The pathophysiology of CAN is intricate and multifaceted. CAN is asymptomatic at first and only shows symptoms in the latter stages of the illness. The identification of people with CAN is crucial because, if detected soon after onset, intensive therapies focusing on lifestyle, glycemic control, and cardiovascular risk factors can delay the disease's course and possibly even reverse it.4

Cardiovascular reflex testing defines the condition subclinically and may have implications for prognosis.5 In terms of clinical associations, autonomic dysfunction is linked to: (1) bradycardia, constant heart rate (more advanced condition); (2) sinus tachycardia; (3) postural tachycardia; (4) cardiac denervation syndrome, orthostatic hypotension with supine (nocturnal) hypertension; (5) decreased exercise tolerance; (6) perioperative and intraoperative cardiovascular instability. The longest autonomic nerve, the vagus nerve, regulates approximately 75% of parasympathetic activity. Since

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autonomic neuropathy initially manifests in the longest fibers, parasympathetic denervation is typically linked to the earliest signs of autonomic neuropathy in diabetes. As a result, early sympathetic tone augmentation characterizes the early development of CAN in diabetes. There aren't many studies on CAN in diabetic patients from western India, and only a few have been conducted in India. As a result, the goal of the current investigation is to ascertain the frequency and contributing factors for CAN in type 2 DM within our specific study design.

Materials And Methods

This prospective observational study, comprising 60 patients, was carried out in a tertiary care hospital for a total duration of 18 months.

Inclusion Criteria

Patients with diabetes mellitus (DM) (type 1 and 2) diagnosed as per American Diabetes Association (ADA).6

Exclusion Criteria

• Additional illnesses linked to the autonomic nervous system (ANS) include severe systemic illnesses (cardiac, pulmonary, renal, and cancer) and thyroid diseases (hyperthyroidism/hypothyroidism). • Individuals taking medications such as beta blockers, sympathomimetics, vasodilators, diuretics, and antiarrhythmics that are known to impair autonomic function.

• Individuals suffering from underlying heart conditions such as arrhythmia, cardiac failure, rheumatic heart disease, ischemic heart disease, and coronary artery disease.

• Patients who are physically incapable and uncooperative.

Demographic details of the patients, such as age, sex, religion, occupation, and residence, were noted. Disease history in detail, duration, and medications used (oral hypoglycemic agents, insulin) were recorded. Presenting complaints with duration and vitals were assessed. A detailed general examination was performed, along with examinations of the central or peripheral nervous system and cardiovascular system. Routine investigations included complete blood count (CBC), renal function tests, serum electrolytes, liver function tests, fasting and random blood sugar levels, urine protein by dipstick, estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD)7 equation, and electrocardiogram (ECG) with QT (corrected) interval.

In addition, special investigations were performed, including fundoscopy for retinopathy, urine protein-to-creatinine ratio, glycated hemoglobin (HbA1c), and fasting lipid profile.

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Our study also included the test for CAN,8 which comprised tests reflecting parasympathetic damage, including: • Resting heart rate. • Heart rate variation during deep breathing (I:E ratio) using ECG—Patients are instructed to breathe six times each minute, taking five seconds to inhale and five seconds to exhale each time.

Calculations are made to determine the difference between the averages of the highest accelerations (inspiration time) and decelerations (expiration time), with the expectation being at least 10–15 breaths per minute. • Valsalva ratio using ECG—Physiological tachycardia is induced by the patient maintaining a mercury column pressure of 40 mm Hg for 15 seconds during expiration. When physiological bradycardia typically develops, the ECG continues to record for 30–45 seconds. The Valsalva ratio is calculated by dividing the greatest heart rate (the shortest RR intervals) by the lowest heart rate (the longest RR intervals). Results with values <1.21 are regarded as abnormal.

Tests for sympathetic damage: • Evaluation of the blood pressure response to standing. • Evaluation of the blood pressure response to sustained handgrip. Followed by this CAN score was calculated,8 and the outcome was categorized as: • Absent—Total points 0. • Early CAN—Points 0.5–1.5. • Definite CAN—Points 2–3. • Severe or advanced CAN—Points ≥3.5. The outcome was determined in terms of CAN score as above.

The five autonomic function tests used to identify CAN, together with the points awarded to the patients based on their results.

Data were gathered and entered into an Excel sheet. Categorical variables were shown as percentages, while continuous data were given as means and standard deviations. When comparing continuous variables, an independent t-test was utilized for normalized data, and a Mann–Whitney test was applied for nonnormalized data. To compare categorical variables, the Chisquared test was used. The Fisher exact test was applied when appropriate for a small number. Where applicable, an analysis of variance (ANOVA) was conducted. Statistical significance was defined as $p < 0.05$. For data analysis, STATA version 14.0 statistical software was utilized.

Results And observations

This study included 60 patients in total. The patients ranged in age from 13 to 75 years with a mean age of 46.4 ± 14.34 years. Of them, 16 were female and 44 were male. With a range of 6 months to 25 years, the mean duration of diabetes was 72.60 ± 22 months . Two groups of patients were created: “without CAN” and “with CAN.”

The patients with CAN were mostly from the older age group ($p = 0.013$), had diabetes for a longer period (78.3 vs 29.14 months; $p < 0.001$), had increased fasting blood sugar

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(p = 0.035), and elevated HbA1c (p = 0.043), in comparison to patients without CAN. CAN-positive patients had a higher prevalence of nephropathy (p = 0.035), retinopathy (p = 0.01), and peripheral neuropathy (p = 0.036) compared to patients without CAN. Also significant was the prolongation of the corrected QT interval in patients with CAN (mean QTc = 443.86 milliseconds in patients with severe CAN compared to QTc = 407.71 milliseconds in patients without CAN).

No significant differences in gender distribution, body mass index, systolic blood pressure, total cholesterol, triglycerides, and creatinine were found between patients with and without CAN. The most frequently observed symptom of diabetic neuropathy was easy fatiguability, seen in nearly 53% of patients. Other symptoms included chronic giddiness and light-headedness, unexplained by other causes, seen in 30% and 16% of patients, respectively. One patient experienced chronic diarrhea, which was attributed to diabetic neuropathy after the exclusion of other causes.

Out of 60 patients, a total of 53 patients (88.3%) with DM had CAN. Of these, 38.3% showed early CAN, 38.3% showed definite CAN, and 7% showed severe CAN. Patients with severe CAN had a mean age of 51.14 ± 10.90 years and a duration of diabetes of 103.71 ± 38.89 months. They also showed higher fasting blood sugar [mean fasting blood sugar (FBS) = 222.57; p = 0.003] and HbA1c (mean HbA1c = 11.26; p = 0.043) compared to patients without CAN. Among those with aberrant cardiovascular autonomic reflex test results, resting tachycardia (heart rate greater than 100 beats/minute) was observed in 40%, abnormal Valsalva ratio (ratio < 1.2) in 73.3%, abnormal E:I difference in 75%, orthostatic hypotension in 31.6%, and abnormal blood pressure response to sustained handgrip in 60% of cases.

Discussion

The prevalence of CAN in our study (88.3%) was slightly higher compared with the study by Birajdar et al. (58%),9 and Mehta et al. (57.5%),10. An abnormal E:I ratio, observed in 75% of patients, was the most common autonomic function test. The prevalence of CAN was reported to be 70% in the study by Bhuyan et al.,8 and the most prevalent CAN anomaly, present in 56% of patients, was an aberrant E:I difference, which is nearly comparable to what we discovered in our investigation. In contrast, a study by Birajdar et al. Reported that 58% of individuals had CAN, with the most prevalent CAN aberration being an abnormal 30:15 ratio, present in 38% of cases. As we included individuals with longterm diabetes (mean duration 72 months), the prevalence of CAN in our study was higher than in earlier studies.

Additionally, the majority of patients in our research center are uneducated, seek medical advice late, and are only diagnosed with DM after developing symptoms. This is particularly true for the suburban population our facility serves. Patients most frequently arrive at our center with a diabetes-related complication. Longer disease

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duration was a substantial predictor of CAN in our sample ($p < 0.001$). However, Chaya Ahire et al. Also suggested that early CAN was frequently observed in patients with a shorter disease duration and concluded that CAN screening should be done on all newly diagnosed type 2 DM patients.

This was also demonstrated in our study, where a cohort with <10 years of diabetes was found to have early CAN, while a cohort with >10 years of diabetes was linked to greater risks of CAN in both the type 1 and type 2 DM cohorts. Despite the cross-sectional nature of the investigation, we found a statistically significant correlation between increased age and CAN in both Type 1 and type 2 DM within our cohort. This finding is consistent with research conducted by Uncontrolled fasting and postprandial blood sugars (PPBS), as well as higher HbA1c, were found to be significantly associated with CAN in our study. This can be explained by the higher risk of accumulation of advanced glycation end products in uncontrolled sugars. Diabetic microangiopathic complications share a similar pathogenesis, making them closely connected.

Our study established that CAN was associated with other microvascular complications, such as peripheral neuropathy, nephropathy, and retinopathy. However, in our study, nephropathy was demonstrated in 79% of patients, neuropathy in 56%, and retinopathy in 58% of patients. Another significant association was observed between QT prolongation and the severity of CAN. Patients with definite and severe CAN had a mean QTc of >440 milliseconds, compared to those with early CAN.

Our study differed from previously conducted studies in that it included patients with all categories of DM (type 1 and type 2). This study is the first of its kind to also include patients who were infected with or had recently recovered from coronavirus disease 2019 (COVID-19); however, the COVID cohort was insufficient to draw definitive conclusions. Additionally, our study established an association between QTc and CAN severity, which can serve as a bedside diagnostic tool.

Conclusion

Cardiac autonomic neuropathy is a frequently overlooked microvascular complication of DM, with our study indicating a prevalence of 88.3%. The findings suggest a predominant parasympathetic over sympathetic nervous system involvement in diabetic autonomic neuropathy, as demonstrated by various diagnostic tests. Among these, the abnormal expiration-to-inspiration (E:I) ratio, observed in 75% of patients, emerged as the most prevalent indicator of parasympathetic dysfunction. Key determinants of CAN include the duration of diabetes, patient age, and the presence of other microvascular complications.

The study also highlighted the clinical utility of QTc interval prolongation on ECG, which, despite its high specificity for diagnosing CAN and assessing its severity, generally

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exhibits low sensitivity. Given the significant association of CAN with increased mortality, it is imperative that all diabetic patients be screened for CAN at diagnosis and subsequently on an annual basis, in alignment with the recommendations from the ADA. Early intervention through optimal glycemic control and lifestyle modifications can play a crucial role in preventing the development of CAN.

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