Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

CLINICO-DEMOGRAPHIC PROFILE OF CORONARY ARTERY DISEASE IN DIABETES PATIENTS WITH CARDIAC AUTONOMIC NEUROPATHY IN A TERTIARY CARE HOSPITAL OF ODISHA

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ABSTRACT:

Objective- To evaluate the clinico-demographic profile of coronary artery disease (CAD) in Diabetes patients with cardiac autonomic neuropathy (CAN). **Material and methods-** This was an observational, prospective study, conducted among diabetic patients with coronary artery disease (CAD) and cardiovascular autonomic neuropathy (CAN) presenting to the Department. of Cardiology, M.K.C.G. Medical College and Hospital, Berhampur, Odisha,India during the period of March 2019 to February 2021. The study population was 100 diabetic patients. **Result-**

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Majority of the patients(59%) were male(not statistically significant), (90%) patients enrolled were type II Diabetes Mellitus, overall prevalence of CAN was 41%, significant proportion of our diabetic patients as well as CAN + patients had asymptomatic ischaemia detected on routine ECG. In our study, the patients with CAN were older and had a longer duration of diabetes and had higher mean age (60.3 ± 9.7 yrs). Higher mean duration of diabetes (11.4 ± 5.5 yrs) in CAN+ patients was highly statistically significant (p = 0.0001). **Conclusion-**In T2DM patients, enhanced glycaemic control can delay development of CAN but increase the risk of severe hypoglycemic episodes, which need to be taken into account when evaluating the risk/benefits ratio.

Keywords-Coronary artery disease, Cardiac autonomic neuropathy, Diabetes Mellitus

INTRODUCTION:

In diabetic patients, the pathophysiology of myocardial ischemia is complex and not fully understood. Some diabetic patients have coronary stenosis obstructing blood flow to the myocardium; others have coronary microvascular disease with an absence of plaques in the epicardial vessels with, or without, endothelial dysfunction. It is important to underline that myocardial ischemia is not synonymous with atherosclerotic coronary disease [**1**]. In the absence of coronary large vessel disease, ischemia is determined by impaired coronary vasodilator reserve and coronary microvascular disease.

The impaired coronary arteriolar vasomotion, including reduced endothelial mediated vasodilation, hypoxia-induced vasodilation, and myogenic response, are the proposed pathophysiologic processes of diabetes-induced coronary microvascular dysfunction **[2].** Both hyperglycemia and insulin resistance, besides TNF-overexpression and inflammation, interfere with flow-mediated endothelial-dependent vasodilation through nitric oxide level decrease and endothelin-1 level increase, which are associated with acute intracellular changes [**2,3,4].** .Furthermore, an inverse correlation was shown between myocardial flow reserve and average levels of HbA1C for five years and fasting plasma glucose concentration, underlining how glycemic control is significantly related to coronary microvascular function **[5].**

Moreover, altered Ca2+ regulation with impaired myofilament function, increased reactive oxygen species formation with decreased antioxidant defenses, raised lipotoxicity, endomyocardial fibrosis, endothelial and cardiomyocyte cell necrosis and apoptosis, and

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autonomic dysfunction are additional mechanisms responsible for cardiomyocyte changes in diabetes mellitus [**2,4].** In diabetes mellitus, chronic hyperglycemia plays a main role in the onset and progression of autonomic neuropathy, which may reduce the vasodilator effect of sympathetic stimulation on coronary resistance vessels [**6**].

One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN**)[7,8,9]** which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics **[10].**

The present report discusses the clinical manifestations (eg, resting tachycardia, orthostasis, exercise intolerance, intraoperative cardiovascular liability, silent myocardial infarction [MI], and increased risk of mortality) in the presence of CAN. It also demonstrates that autonomic dysfunction can affect daily activities of individuals with diabetes and may invoke potentially life-threatening outcomes. CAN may be present at diagnosis, and prevalence increases with age, duration of diabetes, and poor glycemic control.

MATERIAL & METHODS:

This was an observational, prospective study, conducted among diabetic patients with coronary artery disease (CAD) and cardiovascular autonomic neuropathy (CAN) presenting to the Department. of Cardiology, M.K.C.G. Medical College and Hospital, Berhampur Odisha, India during the period of March 2019 to February 2021. The study population was 100 diabetic patients.

Inclusion Criteria:

1. Adult patients (age 18-75 years) with diabetes mellitus
2. Symptomatic or Asymptomatic CAD patients confirmed by invasive coronary angiography
3. Patients with above criteria having Cardiac autonomic neuropathy (CAN)- either diagnosed previously or currently.
4. Only stable patients whose CAN testing is possible.

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Exclusion Criteria:

1. Patients in whom an alternate cause of autonomic dysfunction is suspected (neurological disorder, drugs).

2. Patients with CKD, hypertension, smoking (patients with other CAD risk factors are excluded to avoid baseline confounding and bias in comparing CAN + and CAN - patients with CAD).

3. Patients with advanced heart failure or haemodynamic instability in whom CAN testing isn't possible or inconclusive (shock, hypotension on Ionotropic and O2 support) - only stable patients were included.

STUDY PROTOCOL:

All adult diabetic patients (previously diagnosed cases of DM as per American Diabetes Association guideline already on antihyperglycemic therapy) admitted with symptoms of angina or angina equivalence (midepigastric discomfort, dyspnoea, effort intolerance, excessive fatigue) or symptoms of CAN were initially included in this study. Detailed history was documented (symptoms, signs, comorbidity, addiction, treatment history) and clinical examination was carried out including examination and testing for cardiac autonomic neuropathy.Duration of DM and medication history was recorded. Routine haematological investigation (complete blood count) and biochemical investigation (fasting plasma glucose, renal function test, electrolytes, lipid profile, hs-Trop I) were carried out including HbA1C.

STATISTICAL ANALYSIS: All results for continuous variables were expressed as means ± SD (standard deviation). Data were compared for statistical significance using Fisher's test, Chi-square test, Student's t-test and one-way ANOVA, as appropriate. All analyses were performed using the IBM SPSS statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). A p value <0.05 was considered statistically significant.

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RESULTS:

As per inclusion and exclusion criteria 100 diabetes patients were included in the final analysis

Table 1: Age and Sex Distribution Among study population

Age Groups (in years)	Case(n=100)	
	Male(n=59)	Female(n=41)
<50	11	7
50-70	42	30
>70	6	4

out of which 59 were males (59%) and 41 were females (41%). Majority of the male as well as female patients were in the age group of 50–69 years. Mean age was 59.09±9.7 years. There is no statistically significant difference in age distribution (p=0.2) between males and females

Table 2: Duration and Type of Diabetes Mellitus of study population

Duration Of DM	Type 1	Type 2	Total
≤ 5 yrs	2	24	26
6 to 10 yrs	3	44	47
11 to 15 yrs	2	15	17
≥ 15 yrs	3	7	10
Total	10	90	100

Among the 100 enrolled dibatete patients 10 (10%) were Type 1 and 90 (90%) were Type 2 diabetes patients. Most number of dibaete patients had a duration of diabetes between 6-10 years and next was ≤5 years .

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Table 3: Severity of CAN and Type of Diabetes Mellitus of study population

Type Of DM	Early CAN+	Definite CAN+	Severe CAN+	Total CAN+	CAN-
T1 DM	1	4	2	7	3
T2 DM	15	9	10	34	56
Total	16(39%)	13(32%)	12(29%)	41(100%)	59

Among the 41 (41 %) CAN+ patients, CAN was prevalent in 7 Type 1 diabetes patients and 34 of Type 2 diabetes patients. Early CAN was most prevalent 39% among the study population followed by Definite CAN 32 % and Severe CAN 29%.

Table 4: CAD type with respect to CAN status

CAD Type	CAN+	CAN-	Total	p Value
Chronic Stable Angina	10	21	31	0.27
Old MI	5	12	17	0.4
Asymptomatic Myocardial Ischemia	24	14	38	0.007
Acute Coronary Syndrome	2	12	14	0.03

Majority of CAN positive patients presented with asymptomatic myocardial ischemia (p=0.007) and majority of CAN negative patients had chronic stable angina (p= 0.27).Most of these asymptomatic patients were detected to have CAD from ECG and 2D Echo during routine evaluation and evaluation for atypical symptoms.CAD patients presenting as ACS were less as most patients were unstable and excluded from the study.

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In our study, majority of the study population had asymptomatic myocardial ischemia (38%)followed by chronic stable angina ,old MI and ACS .However there was no significant statistical difference of CAD type among Males and Female patients.

Table 5: Symptoms of CAD and CAN with respect to CAN status

Symptoms	**CAN+**	**CAN-**	**Total**	**p Value**
Angina	14	52	66	0.0001
Dyspnea	34	35	69	0.4
Effort Intolerance	40	49	89	0.05
Fatigue	40	45	85	0.1
Nausea/ Vomiting	30	3	33	0.0001
Cough	27	4	31	0.0001
Silent Ischemia	24	14	34	0.02
Syncope/ Presyncope	14	3	17	0.02
Unawareness of Hypoglycemia	8	1	9	0.04

Most of the CAD patients presented with effort intolerance and fatigue (89% and 85 %) followed by dyspnoea and angina (69% and 66%).However a significantly higher percentage of CAN Positive patients had silent ischemia and CAN symptoms like nausea,vomiting and cough (P=0.0001).

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Table 6: Clinical, Hematological And Biochemical Characteristics with respect to CAN status

Parameters	CAN+	CAN-	Total	p Value
BMI (Kg/m^2)	29.9 ± 3.2	27 ± 7.4	28.2 ± 6.2	0.0204
FBS (mg/dl)	151 ± 28.9	133.3 ± 22.61	140.6 ± 26.7	0.0007
PPBS (mg/dl)	188.5 ± 43.3	166.5 ± 31.7	175.5 ± 38.2	0.0042
HBA1C(%)	8.6 ± 1.7	7.8 ± 1.5	8.1 ± 1.6	0.0147
Hb(gm/dl)	13.4 ± 2.1	13.1 ± 1.9	13.2 ± 1.9	0.374
Create.cle(ml/min/1.73)	95.6 ± 10.2	89.8 ± 10.8	92.2 ± 10.9	0.008
LDL(mg/dl)	134.6 ± 11.5	100.8 ± 13	114.6 ± 20.8	0.0001
HDL(mg/dl)	37.4 ± 8.6	39.9 ± 3.3	38.4 ± 7	0.04
TG(mg/dl)	327 ± 38.8	218.3 ± 47.3	262.9 ± 74.81	0.0001
SBP(mmhg)	133.5 ± 19.3	127.1 ± 21.9	130.9 ± 20.5	0.1
DBP(mmhg)	83.5 ± 91	86 ± 8.7	84.5 ± 9	0.16

The mean BMI,FBS PPBS and HbA1c levels were higher in patients with cardiac autonomic neuropathy (CAN) than patients without cardiac autonomic neuropathy ,the difference was statistically significant. Patients with cardiac autonomic neuropathy (CAN) had higher mean value of LDL and TG compared to patients without cardiac autonomic neuropathy and the difference had very high statistical significance.

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Table 7: Prevalence of CAN in Diabetic Patients

CAN Status	**No. of Patients**
CAN-	59
Early CAN	16
Definite CAN	13
Severe CAN	12
Total	100

The prevalence of CAN was 41% with early CAN in 16%, definite CAN in 13% and severe CAN in 12% of the total study population.

Table 8: CAN status with respect to Age, Sex and Duration of Diabetes Mellitus

Parameters	CAN+	CAN-	Total	p Value
Male	23	36	59	0.6
Female	18	23	41	0.6
Age	60.3 ± 9.7	58.2 ± 9.8	59 ± 9.7	0.2
Duration of DM	11.4 ± 5.5	6.8 ± 3.1	8.7 ± 4.8	0.0001

. Higher mean duration of diabetes in CAN+ patients was highly statistically significant.

DISCUSSION:

Association between Cardiac Autonomic Neuropathy and diabetes have been assessed in several previous studies, however in our search there exists no study comparing association between Cardiac Autonomic Neuropathy and CAD in both type1 and type2 diabetes patients. There was only one study**[11]** which evaluated Cardiovascular Autonomic Neuropathy and subclinical Cardiovascular disease in normo-albuminuric Type 1 diabetes patients. Also there is a lack of studies evaluating severity of CAD and Cardiac Autonomic Neuropathy in diabetes patients. In this present study a total of 100 diabetes patients with CAD were divided into two

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groups having Cardiac Autonomic Neuropathy or no Cardiac Autonomic Neuropathy. The clinical profile of two groups were compared to find any difference in clinical presentation and CAD severity.

Most of the patients were male and the mean age was 59.09±9.7 years. These are corroborative with study **[11,12,13].** In our study of 100 diabetes patients 10% (10/100) were Type 1 and 90% (90/100) were Type 2 diabetes patients. The overall prevalence of CAN was 41% and, the prevalence of CAN was 70% in Type1 diabetes patients and 37.7% in Type 2 diabetes patients similar to study**[11].** There was no significant difference in prevalence of CAN between two sexes which is in accordance with the study **[13]** .

A significant proportion of our diabetic patients as well as CAN + patients had asymptomatic ischaemia detected on routine ECG or while being evaluated for other reasons. Several studies have suggested that silent myocardial ischaemia is more common among diabetic patients than in others **[14,15,16,17] .** A study from Finland showed that at least 9% diabetics had asymptomatic CAD with evidence of active myocardial ischaemia[**18].** However, in our study Silent Myocardial Ischemia (SMI) was 24% in CAN + and 14% in CAN- patients with CAD and diabetes

Angina, the classical symptom of CAD was present more commonly among CAN- patients and a significantly high percentage of CAN+ patients presented with angina equivalent symptoms like effort intolerance, dyspnoea and fatigue .Features of myocardial infarction in patients with CAN may include dyspnea, fatigue, heart palpitations, hypotonia, nausea, and vomiting [**19].** A significant number of with CAN+ patients had nausea/ vomiting and cough and found to have CAD on evaluation.

In our study early, definite and severe CAN was present in 16%, 13% and 12% of patients respectively. The prevalence of CAN was 70%, with early CAN in 25%, definite CAN in 24%, and severe CAN in 21% cases. Among the abnormal cardiovascular autonomic reflex test, resting tachycardia (heart rate ≥100 beats per minute) was present in 17%, abnormal E:I difference in 56%, abnormal 30:15 ratio in 42%, orthostatic hypotension 11%, and abnormal blood pressure response to sustained handgrip in 19% cases . These differences may be because of different inclusion and exclusion criteria. They included only Type2 diabetes patients without CAD.

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In our study, the patients with CAN were older and had a longer duration of diabetes and had higher mean age (60.3 ± 9.7 yrs). Higher mean duration of diabetes (11.4 ± 5.5 yrs) in CAN+ patients was highly statistically significant (p = 0.0001). The positive correlation of CAN and long duration of diabetes have been reported by Ahire et al. [**20**] who demonstrated that patients having duration of diabetes >5 years are more likely to have definite and severe CAN..

In our study higher HbA1c ,FBS,PPBS,BMI were found to be associated with CAN ,which suggests that poor glycemic control does correlate with the prevalence of CAN. No significant differences in sex, SBP, DBP, and HDLwere found between the two groups.Patients with CAN had significantly higher LDL and TG level (p = 0.0001) . However in the study by Ulrik Madvig Mogensen et. al. and Ashok K Bhuyan et. al. there was no significant difference in TG,LDL,HbA1c,FBS,PPBS,BMI levels between the two groups. This deviation may be due to the fact that our study population included both type1 and type2 diabetes patients with more severe CAD. In the study by Ulrik Madvig Mogensen et. al. patients population had subclinical cardiovascular disease with normoalbuminuria with type 1 diabetes. Similarly in the study by Ashok K Bhuyan et. al. patients population were type 2 diabetes patients without CAD.

CONCLUSION:

As the incidence of diabetes rises, so too does the requirement for healthcare, and in order to prevent CAN in patients with T1DM, we must focus on glycaemic control, but in T2DM we should focus not only on glycaemic control but also on improving adherence to cardiovascular risk factor intervention. In T2DM patients, enhanced glycaemic control can delay development of CAN but increase the risk of severe hypoglycemic episodes, which need to be taken into account when evaluating the risk/benefits ratio. There is a need for further studies to discover the optimal level of glycaemic control in order to reduce the development of CAN without increasing the risk of death.

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