CAN and its Risk Factors for Type2 DM

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Research Article

ABSTRACT

Diabetic Neuropathy (DN) is a heterogeneous disorder that encompasses a wide range of abnormalities affecting both proximal and distal peripheral sensory and motor nerves as well as the autonomic nervous system. DN is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life. To determine the association of various risk factors with Cardiovascular Autonomic Neuropathy (CAN) among Type 2 Diabetes Mellitus individuals, a hospital based cross-sectional study was carried out at SRG Hospital associated with Jhalawar Medical College, Jhalawar Rajasthan, during May 2015 to November 2016. The participants were subjected to five non-invasive autonomic function tests as recommended by Ewing's criteria and categorized. There was increase in the prevalence of CAN with increase in the age ($p < 0.001$). This association of different age groups with prevalence of CAN was found to be statistically significant. Gender, smoking, alcohol consumption, family history of diabetes, central and truncal obesity did not shown any significant relation with the prevalence of CAN. Participants consuming mixed diet (65.9% Vs 52.5%) had higher prevalence than vegetarians, which was statistically significant ($p = 0.007$). There was significant association between duration of diabetes and CAN ($p <0.001$) showing progressive increased in CAN with increase in duration of diabetes. The prevalence of CAN in relation with duration of diabetes showed a rising trend. Present study showed a relatively high prevalence of CAN in the study area. In addition, it was also observed that advanced age and duration of diabetes were significantly associated with prevalence of CAN. There is a need to institute screening and awareness programs for early detection, even in rural areas, so as to prevent the development of the long term complications.

KEY WORDS: Cardiovascular autonomic neuropathy (CAN), diabetes mellitus, ewing's criteria

INTRODUCTION:

Type 2 diabetes mellitus [T2DM] (also known as non-insulin dependent diabetes mellitus {NIDDM} or adult-onset diabetes) is non-autoimmune, complex, heterogeneous and polygenic metabolic disease condition in which the body fails to produce sufficient beta cell insulin, impaired insulin effectiveness and characterized by abnormal glucose homeostasis.[1]

Diabetes Mellitus is also well known for the microvascular complications as tripathy includes diabetic neuropathy, retinopathy and nephropathy. An important and common clinical complication of diabetes is diabetic neuropathy (DN). DN is a heterogeneous disorder that encompasses a wide range of abnormalities affecting both proximal and distalperipheral sensory and motor nerves as well as the autonomic nervous system. DN is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life. Most common clinical form of DN is diabetic autonomic neuropathy (DAN) and diabetic peripheral neuropathy (DPN).

There are inconclusive data regarding prevalence of CAN and its reporting. Further, factors that account for the marked variability in reported prevalence rates include the lack of a standard accepted definition, different diagnostic methods used, variability in study selection criteria, population and referral bias.

The prevalence of DN is virtually unknown because the published studies differ considerably with regard to definition, method of assessment and patient selection, despite being considered one of the most common long-term complications of diabetes. Early diagnosis and intervention are of prime importance in preventing potentially serious consequences of diabetic complications. Also, there are not many studies reporting the prevalence of diabetes and autonomic dysfunction among diabetes individuals in

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the rural population. Hence, the present study was carried out to estimate the prevalence and autonomic dysfunction among T2DM individuals in rural population of Southern part of Rajasthan.

MATERIALS AND METHODS:

This was a hospital based cross-sectional studyconducted at SRG Hospital associated with Jhalawar Medical College, Jhalawar, Rajasthan. During May 2015 to November 2016.The study was approved by the JMC Institutional Ethics Committee and Written informed consent was taken from all participants before enrolling into the study. Individuals of age 30 years and above, individuals with symptoms of T2DM and known cases of T2DM (FBG ≥ 126mg/dl) were the inclusion criteria in the study. Exclusion criteria was as follows: (a) Individuals who declined to provide informed consent; (b) Pregnant women / who had delivered a baby weighing ≥ 4.5Kg / women who had gestational diabetes; (c) Individuals with cognitiveneurological, psychological and endocrinal disorders; (d) Individuals with congenital heart diseases; (e) Individuals with T1DM.

The sample size was calculated based on reported prevalence in Rajasthan (11.6%) that are geographically and socio-culturally similar to the study area. Considering absolute error of 5% with 95% confidence level, the sample size was estimated to be 166 using formula n=t2*p(1-p)/e2 .Random Allocation method was used for data collection. The participants were interviewed regarding identification, demographic details, behavioral components, social and biological variables. The subjects were asked to be on overnight fasting (for 8 hrs). Next morning, after confirming fasting, blood glucose was measured. On a pre-informed date, fasting blood glucose (FBS) was estimated (after overnight fast) in morning by using a standard digital glucometer (One touch).All those participants, who had fasting blood glucose more than 126 mg/dl were considered as diabetic as per WHO criteria. FBS was measured by using standard glucometer as per the WHO recommendation for epidemiological purposes.[2] Categorization as per Ewing's and Clarke criteria: - The participants were subjected to five non-invasive autonomic function tests as recommended by Ewing's criteria and categorized.

1. Normal: all five tests normal or one borderline.
2. Early involvement: one of the three heart rate tests abnormal or two borderlines.
3. Definite involvement: two or more of the heart rate tests abnormal.
4. Severe involvement: two or more of the heart rate tests abnormal plus one or both blood pressure tests abnormal or both borderlines.

Data analysis was done by using SPSS 20.0 (Trial version). Differences were considered significant at $p \leq 0.05$ level with confidence interval of (CI) 95%.

RESULTS:

Of the 166 screened participants (mean age of 53.35±9.81 years), majority belonged to age group of 50-59 year (38%), ≥ 60 years (27.1%) and 40-49 years (30.1%) whereas the participants in age group of 30-39 years were least (4.8 %). There were more females (64.5%) than males (Table 1). Nearly half (45.2%) of the participants were illiterate and around one third of them (31.3%) had secondary school education while few had completed primary school education (18.7%) and graduation (4.8%). Majority of participants were farmers (Skilled I - 42.2%) and not involved in active work (Housewives and older people-33.1%). Majority were consuming mixed diet (75.9%). Nearly one-third of the participants were overweight (34.9%) and nearly half of them had truncal obesity (51.2%) and 46.9% had central obesity (Table 2). Prevalence of CAN was found 62.65%. There was increase in the prevalence of CAN with increase in the age ($p<0.001$) (Figure 1). This association of different age groups with prevalence of CAN was found to be statistically significant. Gender, smoking, alcohol consumption, family history of diabetes, central and truncal obesity did not shown any significant relation with the prevalence of CAN. Participants consuming mixed diet (65.9% Vs 52.5%) had higher prevalence than vegetarians, which was statistically significant ($p = 0.007$).

There was significant association between duration of diabetes and CAN ($p <0.001$) showing progressive increased in CAN with increase in duration of diabetes. The prevalence of CAN in relation with duration of diabetes showed a rising trend. Ten factors were analyzed, out of which only 3 potential risk factors (age, diet and duration of diabetes) had significant association with prevalence of CAN in bivariate analysis. Participants with age group of ≥ 60 years were found to have 3.998 times (Otts Ratio) more likely to develop the CAN as compared to all other age groups. Risk of developing diabetes increased with increase in duration of diabetes. Participants with duration >10 years had

5 -10 years had 148.97 fold and < 5 years had 50.438 fold of higher risk for the development of CAN than newly diagnosed (Figure 2).

DISCUSSION:

Prevalence of CAN varies greatly depending on the criteria used for the assessment and the type of population studied. Very few studies have been done on the prevalence of CAN in rural population.

Results of the present study showed high prevalence of CAN among T2DM participants in this region. Various studies from year 1982 -2010 have reported the prevalence of CAN but these have used only one single assessment modality for estimating the prevalence of CAN.[3-4]

In a large cohort study conducted by Ziegler in patients with T1DM and T2DM using predefined heart rate variability (HRV) tests and spectral analysis of the R-R intervals, 25.3% of patients with T1DM and 34.3% of patients with T2DM had abnormal

Table 1: Socio-demographic and Anthropometric characteristic of study participants.

Characteristics	Category	Total Number	Percentage
Age (in years)	30-39	8	4.8
	40-49	50	30.1
	50-59	63	38
	≥60	45	27.1
Gender	Male	59	35.5
	Female	107	64.5
	Total	166	100
Diet	Veg		
	Mixed	40	24.1
	Diet	126	75.9
BMI	<18.5	02	1.2
	18.5-24.9	36	21.7
	25-29.9	73	44.0
	≥30	55	33.1
Central obesity	Yes	77	46.4
	No	89	53.6
Truncal obesity	Yes	85	51.2
	No	81	48.8
	Total	166	100
Smoking	Yes	50	30.1
	No	116	69.9
Alcohol	Yes	44	26.5
	No	122	73.5
Family History of DM	Yes	133	80.1
	No	33	19.9
Total		166	100%

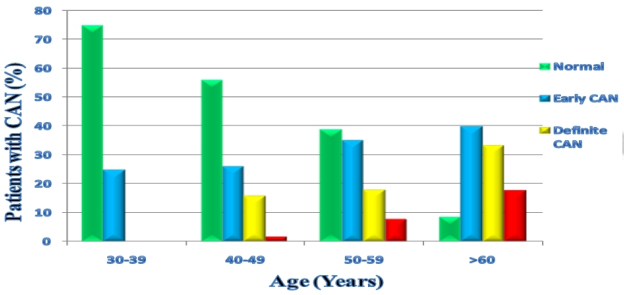

Figure 1: Association between age groups and prevalence of CAN.

findings.[4] In present study by using various cardiovascular reflex tests, the estimated prevalence of CAN was 62.6%. These findings are comparable to the study conducted by Mehta et al in Jaipur, that has reported a prevalence of CAN in 58% of cases, all of them having parasympathetic neuropathy and 20% with sympathetic neuropathy.[5] CAN also accounts for silent myocardial infarction and shortens the lifespan by resulting in death in 25% – 50% of diabetic patients within 5–10 years of CAN.[6]

The European Diabetes Complications Prospective Study (EURODIAB), included 1,101 patients with type 1 diabetes with mean of 7.3 years of duration of diabetes concluded that smoking, glycosylated haemoglobin (HbA1C), diabetes duration and components of the metabolic syndrome (including hypertension, obesity, triglycerides and cholesterol) were associated with an increased risk of polyneuropathy.

Diabetic neuropathy is a heterogeneous disorder not fully explained by a single pathogenic mechanism and its risk factors remain obscure. However, age, duration of disease and degree of glycemic control appear to be strongly associated with diabetic autonomic neuropathy.[7] In T2DM, poor blood glucose control (chronic hyperglycemia) plays an important role both in the initial pathophysiology (oxidative stress, microcirculation dysfunction due to nitric oxide loss and Schwann cell lesion due to accumulation of free radicals) as well as in its progression (axonal degeneration and neuronal apoptosis) of diabetic neuropathy. Results of the present study have shown that risk factors such as age and duration of diabetes had significant association with prevalence of CAN.

In addition, present study also shows that participants with age ≥ 60 years and duration of diabetes >10 years had high risk for developing CAN. Findings of this study are in agreement with those of Voulgari et al. who report that in T2DM patients CAN is independently associated with longer duration of

Table 2: Association between various potential risk factors and prevalence of CAN Ewing tests criteria.

Potential predictors	Sub-Category	Total number	Normal	Early CAN	Definite CAN	Severe CAN	Chi square	p value
Age	30-39	8	6	2	0	0	32.52	<0.001*
	40-49	50	28	13	8	1		
	50-59	63	24	22	12	5		
	≥60	45	4	18	15	8		
Gender	Male	59	18	21	15	5	2.13	0.55
	Female	107	44	34	20	9		
Smoking	No	116	44	40	22	10	1.08	0.78
	Yes	50	18	15	13	4		
Alcohol	No	122	47	39	25	11	0.89	0.62
	Yes	44	15	16	10	3		
Family History of DM	No	33	16	8	7	2	2.63	0.45
	Yes	133	46	47	28	12		
Diet	Veg	40	19	13	5	3	3.36	0.34
	Mixed	126	43	42	30	11		
BMI	< 18.5	2	2	0	0	0	7.02	0.63
	18.5-24.9	36	15	13	6	2		
	25-29.9	73	24	26	18	5		
	=30	55	21	16	11	7		
Central Obesity	No	88	32	30	18	8	0.23	0.97
	Yes	78	30	25	17	6		
Truncal Obesity	No	81	28	27	19	7	0.76	0.86
	Yes	85	34	28	16	7		
Duration of DM	Newly detected	61	59	2	0	0	159.26	<0.001*
	<5 Years	13	2	8	3	0		
	5-10 Years	43	1	25	14	3		
	>10 Years	49	0	20	18	11		

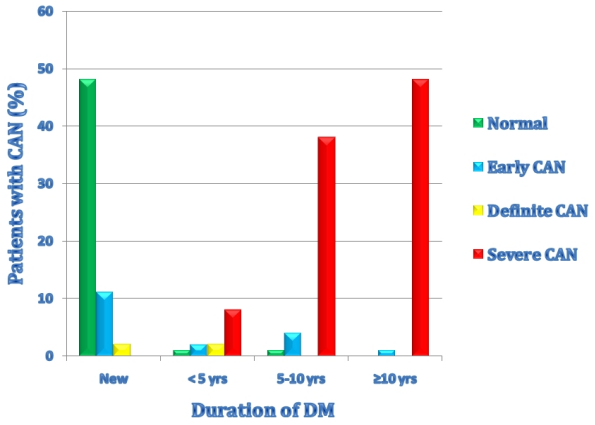

Figure 2: Association between duration of diabetes and prevalence of CAN.

diabetes.[8] Another study conducted by Knuiman et al[9] on 179 individuals with insulin-dependent diabetes mellitus (IDDM), found that age at diagnosis (younger) and duration of diabetes (longer) were important time related risk variables for developing CAN.[10-12] Chronic hyperglycemia and poor glycemic control in diabetic individuals with advanced age and longer duration of disease can lead to production of advanced glycation end-products, disturbances in sorbitol pathway, other metabolic disturbances and increased peripheral resistance due to loss of elastic properties. These will cause nerve damage leading to various types of autonomic dysfunction. Risk of neuropathy increases for diabetics with poor nutrition habits, such as consuming higher fatty foods and being overweight. Present study shows that T2DM participants consuming mixed diet showed higher chances for developing CAN. Similar results were reported by studies conducted by Knuiman M W who had screened 1218 people and found that diet was involved in development of diabetic complication.[9]

Present study further shows that BMI, truncal and central obesity, smoking, alcohol consumption

and family history of diabetes had no significant association with prevalence of CAN among T2DM participants. These results were dissimilar with the study conducted by Christiansen JS (1978) on juvenile insulin dependent diabetes which showed that smoking and alcohol were possible risk factors in pathogenesis of diabetic complication. Similarly, a review study conducted by Vinik I.[4]Aaron in the year 2007 showed that alcohol consumption and obesity may be linked with diabetic complication.[12-15]

CONCLUSION:

A relatively high, higher than the hypothesized, prevalence of CAN was noted in the Jhalawar District. The observations from the present study may be useful in planning, implementation and evaluation of the national health programs such as the National Programs for control of Diabetes, Cardiovascular diseases and Stroke (NPDCS) at local level. High prevalence of CAN in T2DM even in rural community suggests the impact of socioeconomic transition on the occurrence of DM. Advancing age and increasing duration of diabetes appear to be risk factors for development of CAN. There is need to institute screening and awareness programs for early detection of diabetic complication so as to prevent long term complications. The findings of this study suggest the need for the promotion of preventive measures to prevent or delay the development of chronic complications of diabetes through good glycaemic control, regular monitoring, lifestyle modification, practice of exercise and yoga to maintain the normal balance of sympathetic and parasympathetic tone. There is need for research to explore the underlying mechanisms of diabetic neuropathy in T2DM of early onset in particular. Molecular studies may help in understanding the pathogenesis and development of treatment options for diabetic neuropathy.

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