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Original Article

Incidence of cardiovascular diseases and associated risk factors among subjects with type 2 diabetes – An 11-year follow up study

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ABSTRACT

Aims: This study was planned to assess the development of cardiovascular disease (CVD) events over an 11-year period and to identify the associated risk factors that could predict the onset of CVD among subjects with type 2 diabetes.

Methods: Retrospective data of 249 patients (M:F 149:100) with type 2 diabetes, from a cohort of 7800 patients, attending a tertiary care center for diabetes from January 2000 to December 2011 were retrieved and analyzed for this study. Sociodemographic and habitual risk factors, baseline diabetes duration, HbA1c and time of onset of CVD and its risk factors were collected from case records. Person-years method was used to calculate incident rate of CVD. Binary logistic regression analyses were done to identify predictors associated with CVD and its risk factors.

Results: Incidence of CVD among subjects with diabetes was 5.6 cases/1000 person-years. Nearly 60% developed hypertension and dyslipidemia or both during the 11-year period. The most common complication was neuropathy (14.4%). Smoking [OR (95%CI)] [9.26 (1.6–54.9)] ($p = 0.014$) and heavy alcohol consumption [8.7 (1.1–69.8)] ($p = 0.04$) were significantly associated with CVD. Higher BMI was significantly associated with hypertension and dyslipidemia [2.4 (1.3–4.3)] ($p = 0.003$).

Conclusions: Smoking and heavy alcohol consumption were significantly associated with CVD, and increased BMI was significantly associated with hypertension and dyslipidemia among subjects with type 2 diabetes in this study population. These findings emphasize the need for early identification and modification of risk factors associated with CVD events in patients with diabetes.

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1. Introduction

The global burden of diabetes is enormous, with an estimated 366 million people living with diabetes worldwide in 2011.[1] India accounted for nearly one-sixth of global diabetes burden in 2011 with about 62 million people affected by diabetes.[2] Regarding the mortality associated with diabetes, globally there were 4.6 million deaths due to diabetes accounting for 8.2% from all causes of mortality. About 48% of the deaths attributed to diabetes had occurred in the people aged below 60 years. In India, 983,000 deaths were attributed to diabetes in 2011.[1] Cardiovascular disease (CVD) is the major cause of death in diabetes and accounts for one-half of all the deaths due to diabetes.[3] Developing countries like India would bear the greater impact of mortality and morbidity associated with diabetes and CVD, as 70–80% of these deaths are expected to occur in such countries.[4]

A case–control study conducted between subjects with diabetes and those without diabetes in urban South India with a median follow-up period of 6 years compared the mortality rate between the two groups and showed a significant two-fold increase in deaths among subjects with diabetes. The study also reported that mortality rate due to CVD in subjects with diabetes was 52.9%, while it was only 24.2% in the normal counterparts.[5] A retrospective study on the causes of mortality due to diabetes in a tertiary care center from India reported vascular diseases as the foremost cause of death in two age groups i.e. more than and less than 56 years among the hospitalized inpatients.[6] This higher rate of premature deaths in diabetes due to CVD can be attributed to the constellation of recognized risk factors such as elevated blood pressure, increased adiposity and hyperglycemic state.[7]

Numerous studies had reported that the basic changes occurring at the vascular level are mediated through insulin resistance in subjects with diabetes as well as prediabetes.[8] In addition, the role of advanced glycation end products in causing premature atherosclerosis and thereby leading to death has also been reported among Finnish women with diabetes.[9] Insulin resistance has been associated with increased serum levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 and tumor necrosis factor-α, which also play a major role in the vascular endothelial changes in patients with diabetes. Soinio et al[10] reported that patients with type 2 diabetes with high levels of hs-CRP ($\geq$3 mg/l) were more likely to have deaths due to coronary heart disease. Several studies had reported the interlinked pathophysiology behind the increased risk of CVD among patients with type 2 diabetes with inconclusive evidences. Eddy et al[11] had simulated a study based on Archimedes model and reported that 42% of myocardial infarction can be prevented by controlling insulin resistance among young adults.

The above-mentioned studies confirm the strong association of various risk factors, including physiological and inflammatory components, with the development of CVD among patients with diabetes. However, there is a paucity of data on the incidence of non fatal CVD events in subjects with type 2 diabetes in India. Hence, the current study was planned with a primary objective to determine the incidence of non fatal CVD events in patients with type 2 diabetes attending a tertiary care center over a period of 11 years and also to identify its associated risk factors. The secondary objective was to assess the rate of development of CVD risk factors such as hypertension and dyslipidemia and its associated factors among the same cohorts using a retrospective cohort study design.

2. Patients and methods

A retrospective cohort study design was followed to address the research question. There were 7800 patients with type 2 diabetes who visited the outpatient department of a tertiary care center in Chennai, Tamil Nadu, from January to December 2000. Out of the 7800 patients, only 350 patients who had 11 years follow-up details, i.e. till December 2011, were selected for this analysis. Out of 350 patients, 90 subjects who had complications and comorbid conditions associated with diabetes at the baseline and 11 subjects with incomplete data at the baseline were excluded from the analysis. Data of the remaining 249 patients with diabetes, but without any complications and other CVD risk factors (hypertension, dyslipidemia) at baseline and who had undergone annual screening for the presence of complications of diabetes for a period of 11 years were included in this analysis. The details were retrieved from the case records maintained in the medical records department. A schematic representation of the recruitment of subjects is illustrated in Fig. 1. Data from subjects both previously diagnosed with diabetes, and diagnosed in the year of 2000 were included in the study.

Socio-demographic details viz., age, gender, habitual risk factors such as smoking and alcohol consumption, baseline HbA1c, BMI, duration of diabetes and family history of diabetes were collected from their case records. The development of CVD risk factors such as hypertension and dyslipidemia during the 11 years, if any, was noted and their time of onset from the baseline was also recorded. JNC VI and VII criteria was followed for the diagnosis of hypertension and similarly, successive NCEP ATP guidelines were used in diagnosing dyslipidaemia.[12,13] The occurrence of disorders pertaining to CVD such as angina, coronary heart disease, peripheral arterial disease and stroke in the subsequent years from 2000 to 2011 was recorded from their case records with a confirmative diagnosis made by the physicians. The tertiary care center follows ADA criteria for the diagnosis of diabetes and its complications.[14]

The study subjects were categorized into current smokers, ex-smokers and non-smokers based on their details in their case records. Non-smokers were those who have never smoked in their lifetime. Ex-smokers were those who had smoked previously and stopped smoking at least 6 months prior to the baseline. Current smoker was defined as a person who had the habit of smoking regularly. Similarly, alcohol consumers were also grouped into 3 categories viz., abstainers group (never consumed alcohol), consumed alcohol occasionally (taking alcohol in moderate level and the frequency of consumption is also less than once a week), and heavy drinkers (who consumed alcohol for almost all the days in a week and the quantity of consumption exceeds 50 ml in male and 30 ml in female per drink).

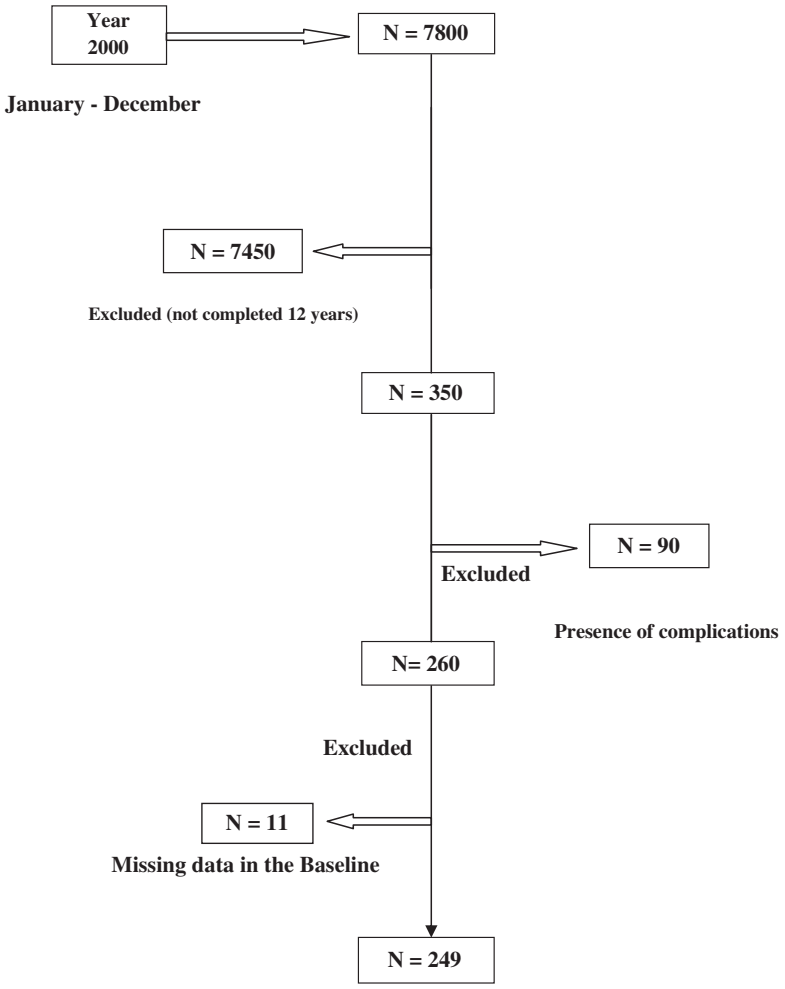

Fig. 1 – Schematic representation of selection of study subjects.

2.1. *Statistical analysis*

Mean and standard deviation were reported for continuous variables, and frequencies and proportion were reported for categorical variables. The incident rate of CVD among the study cohort was calculated using person-years method. Binary logistic regression analysis was done with the development of CVD events vs. non development of CVD events as dependent variable and the independent variables were age (continuous variable), gender (Male vs. female), baseline BMI (<25 vs. ≥ 25 kg/m^2), HbA1c [$<7.5\%$ (<58 mmol/mol) as reference group vs. ≥ 7.5–9% (≥ 58–75 mmol/mol) vs. $\geq 9\%$ (≥ 75 mmol/mol)], duration of diabetes (<5 years as reference group vs. 5–10 and ≥ 10 years), positive family history of diabetes, smoking habit and alcohol consumption. Another binary logistic regression was done with the above-mentioned independent variables and presence of CVD risk factors (hypertension and dyslipidemia) vs. absence of CVD risk factors as dependent variable to identify the associated factors. Statistical software SPSS version 16.0 was used for all the statistical analyses. A p value of <0.05 was considered to be statistically significant.

3. Results

Data of 249 subjects (149 males and 100 females) with type 2 diabetes from the cohort of 7800 patients during the entire period of 11 years were analyzed in this study. The mean age of the study subjects at baseline was 55.6 ± 9.7 years and the median duration of diabetes at baseline was 2 years, ranging from 0 to 19 years. About 64.7% had a positive family history of diabetes. Regarding the habitual risk factors, 82.3% were non-smokers, 11.2% were current smokers and another 6.4% were ex-smokers. Nearly 90% of the study subjects never consumed alcohol, 7.6% consumed alcohol occasionally and 3.2% were heavy drinkers. At baseline, 63.4% were on OHA, 0.4% on insulin and 36.2% were on both OHA and insulin. The average HbA1c of the study subjects at baseline was $9.5 \pm 2.4\%$ (80 ± 26.2 mmol/mol) (Table 1).

3.1. *Incidence of CVD among subjects with type 2 diabetes*

The incident rate of CVD among the study subjects was 5.6 cases/1000 person-years (95% CI; 3.14–9.26). Among the

Table 1 – Baseline characteristics of the study subjects.

Characteristics	Values
N (M:F ratio)	249 (149:100)
Values are mean ± SD	
Age (yrs)	55.6 ± 9.7
HbA1c [% (mmol/mol)]	9.48 ± 2.44 (80 ± 26.7)
Duration of DM (yrs)[a]	2 (0–19)
Values are n (%)	
Positive family history of DM	161 (64.7)
Smoking	
Non smoker	205 (82.3)
Ex-Smoker	16 (6.4)
Regular	28 (11.2)
Alcohol	
Never	222 (89.2)
Occasional	19 (7.6)
Regular	8 (3.2)
Body mass index (BMI) kg/m^2	
Mean BMI	26.8 ± 4
≥25 kg/m^2	164 (65.9%)
Type of medication	
OHA	158 (63.4)
Insulin	1 (0.4)
Both	90 (36.2)

[a] Median (range).

selected study cohort, 15 subjects had developed non fatal CVD events during the 11-year period, of which 12 (80%) were males and 3 (20%) were females. The median period of development of CVD events was 6 years with a range from 2 to 11 years. The most common reported CVD was peripheral arterial disease (4%), followed by angina (1.6%) and congestive cardiac failure (0.4%). All those who had developed angina were males and only one female had developed congestive cardiac failure. There was no significant gender difference in the CVD events ($p = 0.08$).

Microvascular complications including retinopathy, neuropathy and nephropathy were observed in 52 (20.9%) subjects as shown in Table 2. Among all the complications, the most commonly occurring complication was neuropathy in the study cohort. There was no significant gender difference in the onset of these complications as observed in the case of development of CVD. The proportion of male and female patients with complications is shown in Fig. 2. Although there was no significant association between gender and development of neuropathy, there was a higher rate of development of neuropathy and PVD in males compared to females.

Irrespective of the presence of other complications, 59.4% of the study cohort had developed hypertension and/or dyslipidemia within the time period of 11 years. The proportion of

Table 2 – Development of CVD events and other complications over the 11-year period among the study subjects.

Presence of complications and comorbid conditions	% [95% CI]
CVD events	6 [3.1–9]
Other microvascular complications	20.9 [15.9–26]
Hypertension and/or dyslipidemia	59.4 [53.3–65.5]

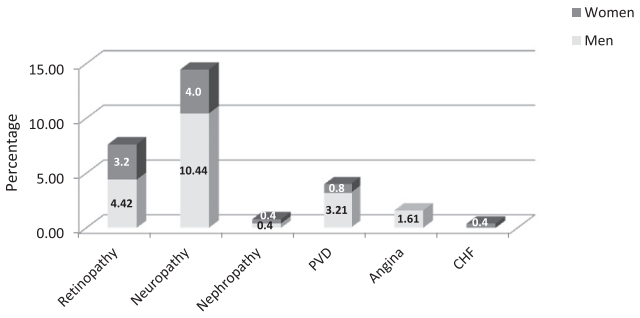

Fig. 2 – Gender wise details on proportion of subjects who developed diabetes related complications.

male subjects (60.1%) that developed hypertension and/or dyslipidemia was higher than that of the females (39.9%), but it was not statistically significant. There was no significant correlation between age and the development of hypertension and dyslipidemia ($p = 0.91$). There were 52 (20.8%) of the study subjects who did not develop any complication or comorbid condition related to diabetes.

Binomial regression analysis showed that smoking habit and alcohol consumption were significantly associated with development of CVD events as given in Table 3. Current smokers had recorded a higher odds ratio (OR) of 9.3 compared to subjects without smoking habit ($p = 0.014$). Similarly, those who were consuming alcohol heavily had an OR of 8.7 for the development of CVD events compared to those who never consumed alcohol ($p = 0.04$).

The regression analysis also revealed those with BMI ≥25 kg/m^2 at baseline were almost 2.5 times at higher risk of developing hypertension and dyslipidemia in comparison with those who had BMI<25 kg/m^2 ($p = 0.003$). All the other independent variables such as age, sex, positive family history of diabetes, duration of diabetes, HbA1c categories, smoking and alcohol consumption did not show any statistically significant association with the development of hypertension and dyslipidemia (Table 4).

4. Discussion

This retrospective cohort study on patients with type 2 diabetes for a period of 11 years revealed that there is a greater

Table 3 – Result of Binomial logistic regression analysis. Dependent variable: (CVD events vs. non-CVD).

Significant variables	β	S.E	Odds ratio (95% CI)	p value
Non-smokers (reference group)				
Ex-smokers	−1.39	1.3	0.25 (0.02–3.1)	0.280
Current smokers	2.23	0.9	9.26 (1.6–54.9)	0.014
Abstinence from Alcohol (reference group)				
Occasional consumers	−19.2	1.34	0.01 (0.001–0.1)	0.9
Heavy drinkers	2.16	1.06	8.7 (1.1–69.8)	0.04

Non-significant variables: age, sex, family history of diabetes, duration of diabetes, HbA1c, and BMI.

Table 4 – Result of binomial logistic regression analysis. Dependent variable: presence of CVD risk factors (hypertension and dyslipidemia) vs. absence of CVD risk factors.

Significant variables	β	SE β	Odds ratio (95%confidence interval)	p value
BMI (<25 kg/m^2) reference group ≥25 kg/m^2	0.882	0.29	2.4 (1.3–4.3)	0.003

Non-significant variables: age, sex, family history of diabetes, duration of diabetes,, HbA1c, smoking habit and alcohol consumption.

risk for the occurrence of CVD, particularly peripheral arterial disease. Another important highlight of the study was that about 60% of the patients had developed either hypertension or dyslipidemia or both during this period.

About 6% of the subjects had developed non fatal CVD over a period of 11 years. Although there was no significant difference between male and female in the development of CVD, the pattern of incidence of certain CVDs such as angina was predominantly found in males except for only one female patient who had developed congestive cardiac failure.

Current smokers were 9 times at higher risk of developing CVD than non-smokers and the association between CVD and ex-smokers was not significantly associated with CVD among the study subjects. Such an observation showing the high risk of developing macrovascular complications among smokers with diabetes has been previously reported.[15]

Similarly, patients with heavy consumption of alcohol also had an eight-fold higher risk of developing CVD than those who never consumed alcohol. A recent study also showed a similar result that the risk of developing CVD, particularly stroke, was significantly high among hypertensive individuals with a habit of heavy alcohol consumption.[16]

In the current study, duration of diabetes was not found to be associated with CVD events. Even the UKPDS had reported a weaker association between duration of diabetes and incidence of CVD in subjects with diabetes.[17] In the present study, at baseline, nearly 70% of the study subjects had duration of diabetes less than 5 years, 17.35% of subjects had duration between 5 and 10 years and 12.8% of subjects had duration of diabetes more than 10 years. The interesting finding in this study was all subjects who had developed CVD had duration of diabetes less than 10 years at baseline. Such a link between clustering of CVD risk factors and early onset of diabetes was observed in a group of individuals with recently diagnosed diabetes in a case–control study conducted in South Carolina.[18]

Baseline HbA1c values were not significantly associated with CVD among the patients in contrast to the results reported by Selvin et al[19] In the present study, at baseline, most of the study subjects, nearly 58%, had HbA1c ≥9% (≥75 mmol/mol) and another 17.7% had their HbA1c between 7.5 and 9% (58–75 mmol/mol), indicating poor glycemic control among the study subjects, though they had not developed any complications associated to diabetes. This observation may be carefully interpreted since follow-up HbA1c values were not recorded in this study, which would have an impact on the development of CVD. Nevertheless, several pharmacological interventional trials have also reported a non-significant reduction in CVD-related events with a reduction in glycated hemoglobin.[20–22]

Another important finding of this study was that patients with type 2 diabetes and with BMI ≥25 kg/m^2 were twice at risk of developing hypertension and dyslipidemia even after adjusting for all confounding variables. This finding reiterates that obesity plays a major role in the grouping of most of the CVD risk factors among patients with diabetes. In this context, the positive effects of body weight reduction on CVD risk factors such as systolic and diastolic blood pressure and other lipid parameters and glycemic control have been reported in the Look AHEAD trial conducted among 5145 patients with diabetes.[23]

The association of modifiable risk factors such as smoking habit, excessive alcohol consumption and increased BMI with CVD and its risk factors and the effect of intensive lifestyle intervention on reduction of CVD risk factors, as observed in Look AHEAD trial, clearly state that a comprehensive treatment comprising pharmacological management of diabetes and intensive lifestyle modification for behavioral changes is necessary to control the huge burden of CVD associated with the exponential increase in the prevalence of diabetes in India.

The most common complication developed among the study subjects was neuropathy (14.4%), followed by retinopathy (7.6%) and CVD (6%). Similarly, Maji et al[24] have reported neuropathy to be an earlier and commonly occurring complication among subjects with diabetes in India.

The study has few limitations. Only non-fatal CVD events had been taken into account and there is a possibility of fatal CVD during the 11 years period among the excluded subjects, which could not be retrieved from medical records. Moreover, the other parameters such as increased waist circumference, diet and physical activity adherence were not considered because of non-availability of these data. Although this analysis is of retrospective type, it confirmed the strong association of smoking and alcohol consumption and higher BMI with CVD or its risk factors among subjects with diabetes. In addition, it has to be noted that there is a scarcity of studies looking at such an association in patients with diabetes. Hence, the present findings add further knowledge to the existing literature on the link between risk of developing non-fatal CVD events and habitual risk factors such as smoking and heavy alcohol consumption, especially in people with diabetes.

5. Conclusions

In conclusion, the incident rate of non-fatal CVD events among subjects with type 2 diabetes was 5.6 cases/1000 person-years. Smoking habit and alcohol consumption were significantly associated with CVD events in Indian patients with type 2 diabetes. In addition, obesity is strongly associated with the development of clinical CVD risk factors such as dyslipidemia and hypertension. Habitual risk factors and obesity correction through lifestyle management should be taken up with high priority and periodically reinforced among

these patients to delay or prevent the development of CVD and its risk factors.

Conflicts of interest

All authors have none to declare.

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