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# SMOKING AND RISK OF CORONARY HEART DISEASE AMONG WOMEN WITH TYPE 2 DIABETES MELLITUS-A PROSPECTIVE STUDY AT TERTIARY CARE HOSPITAL FROM NORTH INDIA

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## ABSTRACT

Although the association between smoking and increased risk of coronary heart disease (CHD) is well established in the general population but this relationship is less well-defined among individuals with diabetes.In this study,we aimed to assess the relationship between cigarette smoking and risk of CHD among women with type 2 diabetes mellitus. All women diabetics reporting to Medicine dept of Dr Dr RML Institute of Medical Sciences, Lucknow, India for their treatment were included in this study. There were total of 1637 women diagnosed as having type 2 diabetes mellitus. All these diabetic women were assessed for CHD as main cardiac outcome in this study. We documented 115 incident cases of CHD (50 fatal CHD-related cases and 65 nonfatal myocardial infarctions). We found a dose-response relationship between current smoking status and risk of CHD among diabetic women. Compared with never smokers, the relative risks (RRs) for CHD were 1.21 (95% confidence interval [CI], 0.97-1.51) for past smokers, 1.66 (95% CI, 1.10-2.52) for current smokers of 1 to 14 cigarettes per day, and 2.68 (95% CI, 2.07-3.48) for current smokers of 15 or more cigarettes per day in multivariate analyses (P<.001 for trend). The multivariate RR of CHD among diabetic women who had stopped smoking for more than 2 years was similar to that among diabetic women who were never smokers (RR, 1.01; 95% CI, 0.73-1.38). In secondary analyses involving diabetic and nondiabetic women, the multivariate-adjusted RR of CHD for those with diabetes who currently smoked (≥15 cigarettes per day) compared with those who never smoked was 7.67 (95% CI, 5.88-10.01).Cigarette smoking is strongly associated with an increased risk of CHD among women with type 2 diabetes mellitus. Furthermore, quitting smoking seems to decrease this excess risk substantially; women with diabetes should be strongly advised against smoking. Diabetes confers a substantially increased risk of coronary heart disease (CHD).[1,2,3] especially among women.[4,5] Smoking is an established risk factor for CHD among the general population.[6,7] However, the magnitude of the association between smoking and CHD risk among diabetic women has not been well studied.[7,8] Furthermore, the impact of quitting smoking, using quantitative measures of quitting history, on this CHD risk has not been investigated fully. Therefore, we assessed the relationships of smoking and quitting smoking to the risk of CHD among diabetic women.

## SUBJECTS AND METHODS

Total registered diabetic women were 1637 aged 30 to 55 years. This information has been updated every 4 months. The population for this analysis included women who were diagnosed as having type 2 diabetes mellitus at baseline or during follow-up between Apr2017 to Apr 2020.Smoking status was assessed on each 4th monthly review. Participants were classified as current, past, or never smokers. Current smokers were categorized into those who smoked 1 to 4, 5 to 14, 15 to 24, 25 to 34, 35 to 44, or 45 or more cigarettes per day. In this study, these categories were collapsed into 1 to 14 and 15 or more cigarettes per day because of the small number of cases. For time since quitting, former smokers were categorized as having stopped smoking for 1 to 5, 6 to 10, 11 to 15, and more than 15 years. The last 2 categories were also combined to assess the effect of quitting for more than 03 years. Coronary heart disease related events were allocated to the smoking exposure status defined on the most recent questionnaire.When a participant reported a diagnosis of diabetes, we mailed her a supplementary questionnaire requesting

information on the details of the diagnosis (ie, diagnostic tests, symptoms, and year of diagnosis) and therapy (insulin or oral hypoglycemic treatment). Using the National Diabetes Data Group criteria, diabetes was considered confirmed if the questionnaire indicated one of the following: (1) classic symptoms (excessive thirst, polyuria, weight loss, and hunger) associated with an elevated plasma glucose level (fasting value, ≥126 mg/dL [≥7.8 mmol/L]; random value, ≥200 mg/dL [≥11.1 mmol/L]; or a ≥2-hour postglucose challenge value of ≥200 mg/dL [≥11.1 mmol/L]); (2) there were no symptoms, but at least 2 plasma glucose values were elevated by the criteria previously described on different occasions; or (3) treatment with a hypoglycemic medication (insulin or an oral hypoglycemic agent).We depended on self-reported information for the diagnosis of diabetes by these patients, but validated the reports in a random sample of women by obtaining their medical records. Among 21 women classified by the supplementary questionnaire as having type 2 diabetes mellitus, 18 provided permission to review their medical records and 16 had records available. A principal investigator blinded to the information reported on the supplementary questionnaire reviewed the records according to the National Diabetes Data Group criteria[8] The diagnosis of type 2 diabetes mellitus was confirmed in 15 (98%) of the 16 women[9]Those with diabetes diagnosed before the age of 30 years (most likely type 1 diabetes mellitus) or a previous diagnosis of cancer or cardiovascular disease (CVD) were excluded from all analyses. In the primary analyses, self-reported diabetes was used to define the analytic cohort (n = 1637 diabetic women). Secondary analyses including only diabetic cases confirmed by the supplementary questionnaire (n = 1216) yielded similar resultsThe primary end point in our analysis was incident Coronary Heart Disease (CHD) (including nonfatal myocardial infarction [MI] and fatal CHD). We analyzed stroke and total CVD (CHD and stroke) as secondary end points. All CVD-related cases were included in the analysis if they were diagnosed after the diagnosis of diabetes. Women who reported a nonfatal MI were asked permission to review their medical records, which were used to confirm the diagnosis according to the World Health Organization diagnostic criteria (ie, symptoms plus either cardiac enzyme (Troponin) level elevations or diagnostic electrocardiographic changes). Physicians blinded to exposure status conducted the record reviews. Infarctions were classified as probable if a patient required hospital admission, and confirmatory information was obtained by interview or letter without medical records. All confirmed and probable nonfatal MI cases were included in the analyses.Fatal CHD cases were ascertained by reviewing the institute-hospital vital records and by a search of the National Death Index. This search was supplemented by reports from the next of kin, and their written permission was sought to review the medical records. Fatal CHD was defined as a fatal MI if confirmed by hospital records or autopsy or as a CHD-related death when recorded on the death certificate if this was the underlying and most plausible cause and there was previous evidence of CHD. We designated as presumed fatal CHD those cases in which CHD was the underlying cause on the death certificate but no records were available. Also included under fatal CHD were cases of sudden death (within 1 hour of the onset of symptoms) with no plausible explanation other than CHD.Stroke was defined according to the National Survey of Stroke criteria.[10] by the presence of a typical neurological deficit of sudden or rapid onset, persisting for more than 24 hours or until death. Stroke classifications included ischemic stroke due to thrombotic or embolic occlusion of a cerebral artery or rupture of a vessel resulting in subarachnoid or intraparenchymal hemorrhage. Vascular disease due to traumatic, neoplastic, or infectious processes was excluded Participants contributed person-time from the date of diabetes diagnosis (for those with incident diabetes) until the date of occurrence of MI, the date of death from CHD or whichever came first. Incident cases of CHD were allocated to the exposure status defined in the most recent questionnaire. For comparison of the excess risk of smoking among diabetic and nondiabetic women, incidence rates of CHD were calculated by dividing the number of new cases by the cumulated person-time of follow-up and were adjusted to the age distribution of diabetic and nondiabetic women by direct standardization. Relative risks were calculated as the incidence rate in each smoking category divided by the corresponding rate among never smokers. All relative risks (RRs) were age adjusted, and 95% confidence intervals (CIs) were calculated.Pooled logistic regression models with 6 months increments were used to control simultaneously for known CHD risk factors. Most of the covariates were updated biennially, including age (<50, 50-54, 55-59, 60-64, or ≥65 years); postmenopausal hormone use (premenopausal status, never used, current use, or past use); alcohol use (0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d); duration of diabetes (0-5, 6-10, 11-15, or >15 years); body mass index, calculated as weight in kilograms divided by the square of height in meters (21, 22, 23-24, 25-28, or ≥29); physical activity (<1, ≥1-<2, ≥2-<4, ≥4-<7, or ≥7 h/wk of moderate to vigorous activity); diabetes medication (assessed in the supplementary diabetes questionnaire : none, oral medication only, or insulin use); history of high cholesterol (yes or no); history of high blood pressure (yes or no); and parental history of MI before the age of 60 years assessed as yes or no).Several dichotomous variables were used for stratified analyses to assess potential effect modification: body mass index (<25 or ≥25kg/m2), insulin use (yes or no), parental history of MI (yes or no), postmenopausal hormone use (yes or no), alcohol use (yes or no), duration of diabetes (≤10 or >10 years), physical activity (<3.5 or ≥3.5 h/wk), age (<60 or ≥60 years), aspirin use (yes or no), and menopause status (premenopausal or postmenopausal). In an additional analysis, we examined the joint effects of smoking and diabetes on the risk of CHD.Values of covariate that were not collected in a given follow-up questionnaire

were carried over from the previous questionnaire or carried backward for covariates not recorded at baseline. Tests for trend were conducted using the median value for each category of smoking status as a continuous variable. All P values were 2-sided. The SAS statistical software package was used for the analyses.[12]

## RESULTS

Data shows the characteristics of the diabetic women in relation to their smoking habits. Current smokers were leaner and more likely to consume alcohol. Past smokers had a higher prevalence of diagnosed high blood pressure. Current smokers were less likely to use vitamin E supplementation. The risk of CHD increased monotonically with greater smoking. Compared with never smokers, the RRs for CHD were 1.21 for past smokers, 1.66 for current smokers of 1 to 14 cigarettes per day, and 2.68 for current smokers of 15 or more cigarettes per day in the multivariate analysis. The association for nonfatal MI was somewhat stronger than for fatal CHD. Further adjustment for vitamin E supplement use did not alter the results. Current smokers had an RR of 2.17 of developing CHD compared with nonsmokers (never or past smokers) in multivariate-adjusted analyses, and the CHD risk attributable to smoking in this population was 19% .Analyses stratified by body mass index, parental history of MI, postmenopausal hormone use, diabetes medication, duration of diabetes, and alcohol use showed consistent association between smoking and risk of CHD. This association was stronger among women younger than 60 years than among women 60 years and older. Past smokers were divided into those who stopped smoking for more than 15, 11 to 15, 6 to 10, and 1 to 5 years (Figure 1). The multivariate RR of CHD among diabetic women who had stopped smoking for more than 10 years was similar to that among diabetic women who were never smokers. Women who had stopped smoking within the past 10 years still had an increased risk (RR, 1.32 [95% CI, 0.96-1.84] for those who quit for 6-10 years; and RR, 1.40 [95% CI, 1.04-1.88] for those who quit for 1-5 years) compared with the never smokers. Nevertheless, the latter 2 groups of past smokers were still at a lower risk compared with current smokers. In secondary analyses, we examined smoking in relation to the risk of stroke and total CVD (stroke and CHD). The multivariate RRs for stroke were 0.69 (95% CI, 0.48-1.00) among past smokers, 1.04 (95% CI, 0.50-2.17) among current smokers of 1 to 14 cigarettes per day, and 1.84 (95% CI, 1.21-2.81) among current smokers of 15 or more cigarettes per day (P = .004 for trend). The multivariate RRs of CVD were 1.03 (95% CI, 0.86-1.25) for past smokers, 1.46 (95% CI, 1.02-2.10) for current smokers of 1 to 14 cigarettes per day, and 2.42 (95% CI, 1.94-3.02) for current smokers of 15 or more cigarettes per day (P<.001 for trend).We also compared age-adjusted rates of CHD in women with diabetes with those in nondiabetic women according to smoking status. The age-adjusted incidence rate of CHD among diabetic women was much higher than that of nondiabetic women of similar smoking status (Figure 2). The joint impact of smoking and diabetes status on the risk of CHD was substantial; compared with nondiabetic women who had never smoked, diabetic women who smoked 15 or more cigarettes per day had an age-adjusted RR of 19.01 (95% CI, 15.42-23.45). This RR was attenuated to 7.67 (95% CI, 5.88-10.01) in the multivariate-adjusted model. Among nondiabetic women, the multivariate RR comparing current smokers (≥15 cigarettes per day) with never smokers was 5.13 (95% CI, 4.53-5.80). The corresponding RR among diabetic women was 2.65 (95% CI, 2.06-3.40). The likelihood ratio test and interaction was significant (P<.001). The higher RR of CHD of nondiabetic women who smoked compared with diabetic women who smoked can be explained by the much higher baseline risk of diabetic women compared with nondiabetic women.

## DISCUSSION

We observed a strong positive association between cigarette smoking and CHD among diabetic women. Cigarette smoking amplified the excess risk of CHD associated with type 2 diabetes mellitus. On the other hand, smokers who quit smoking for more than 10 years had a risk of developing CHD similar to that of diabetic women who had never smoked. The strengths of the study include the large number of diabetic women and the long duration of follow-up, which allows the assessment of smoking and CHD risk in different subgroups. The follow-up rate for fatal and nonfatal events was high (approximately 98%), minimizing potential bias due to loss to and unavailability for follow-up. The prospective design minimized selection and recall bias, which can occur in case-control studies. Potential weaknesses should be noted. Some women with diabetes may have been undiagnosed in the cohort because we did not screen for glucose intolerance. However, these cases would not alter the case status of women reporting a diagnosis of diabetes, which was validated in a separate study.[9] The smoking assessment was based on self-reports and was not verified by other objective measures. However, reporting of smoking should not be biased in relation to CHD incidence because smoking was assessed before the development of CHD. In addition, because the smoking variable was updated every 4 months, our analyses were able to take into account changes in smoking behavior. Few previous studies have prospectively examined the association between smoking and CHD among diabetic persons. A Finnish prospective study.[14] among 313 men and women with type 2 diabetes mellitus did not find smoking to be related to fatal or nonfatal CHD in a univariate logistic regression analysis. Also, in the Whitehall study.[15,16] smoking was not significantly associated with CHD-related mortality rates among 224 diabetic and glucose-intolerant men. Both studies involved fewer diabetic subjects and had a shorter follow-up than our study; thus, statistical power to detect an association was limited[17]. On the other hand, in the National Health and Nutrition Examination Survey study

CHD-related mortality risk was higher among 492 diabetic smokers compared with never smokers, and in the Multiple Risk Factor Intervention Trial[17] risk of CVD-related mortality among 5625 diabetic men increased with higher levels of smoking. This was also supported more recently by the results from the United Kingdom Prospective Diabetes Study,18 in which smoking was a significant risk factor for fatal and nonfatal MI (P = .02) among diabetic women and men in multivariate analyses. Diabetes may increase the risk of CHD through various proposed mechanisms, including lipoprotein changes, increased vascular endothelial injury and permeability, thrombotic disorders, increased oxidative stress, and fibrinolytic factors and platelet activities leading to atheroma formation,[19,20,21] Smoking may exacerbate these conditions and contribute to a dramatically increased risk of CHD among diabetic persons by a combination of short-term effects (coronary artery spasm, arrythmias, and increased platelet aggregation) and long-term effects (increased triglyceride levels, decreased high-density lipoprotein levels, and other metabolic effects that lead to atherogenesis)[19,22] on the cardiovascular system. Smoking is also thought to increase insulin resistance and aggravate metabolic disturbances among diabetic persons,[23,24] Targher et al,[25] for example, found among 40 diabetic patients that insulin resistance was markedly aggravated among smokers. In previous studies, smoking 25 cigarettes per day or more, compared with never smoking, was associated with a higher risk of developing diabetes among women (RR, 1.42; 95% CI, 1.18-1.72)26 and men (RR, 1.94; 95% CI, 1.25-3.03).27Our results also indicate that diabetic women who smoked 15 or more cigarettes per day had an 84% higher risk of developing stroke compared with never smokers. These results are consistent with earlier findings,[9] that smoking amplifies the risk of stroke among diabetic women.[28] Quitting smoking and maintaining cessation for more than 10 years seem to substantially reduce the high risk of developing CHD among diabetic women who smoked. The benefits of smoking cessation are associated with total mortality rate,[28] with CHD and stroke incidence among the Nurses' Health Study and general populations and, more recently, with CHD risk in the United Kingdom Prospective Diabetes Study cohort of diabetic persons The United Kingdom Prospective Diabetes Study found that, compared with never smokers, past smokers were at lower risk of nonfatal and fatal MI (RR, 1.27) than current smokers (RR, 1.74). However, that study did not provide detailed analysis of past smokers according to the duration of quitting and its association with CHD risk. The American Diabetic Association recently emphasized the importance of targeted smoking cessation programs for diabetic persons, calling for health care providers to (1) routinely assess tobacco use among diabetic persons, (2) counsel on smoking prevention and cessation, and (3) routinely implement smoking cessation guidelines. Although smoking rates were slightly lower among the diabetic women in our study compared with the nondiabetic population, it is alarming that others found smoking rates among diabetic persons to be similar to24 or even higher than those of nondiabetic persons. However, individuals with diabetes seem to be more receptive to their physician's advice and to the prospect of smoking cessation Smoking cessation may have an important effect on CHD risk reduction among diabetic persons compared with the effects reported with cholesterol lowering or high blood pressure treatment. Clinical trials to lower cholesterol levels among diabetic persons achieved 25% to 55% reduction in the risk of major CHD-related events,[37,38] and tight blood pressure control achieved 21% reduction in the risk of fatal and nonfatal MI and sudden death (although the results were not statistically significant).[39] Our results suggest that the risk of CHD among diabetic women who smoke could have been reduced by about 54% if they had not smoked. In the overall diabetic population, which comprises 20% smokers, the population attributable risk due to current smoking was 19%.Our findings have important clinical and public health implications and provide strong support for the American Diabetic Association recommendations. Given that cigarette smoking is such a strong, yet modifiable, risk factor for CHD among diabetic individuals, physicians should discourage their diabetic patients from smoking.

## CONCLUSIONS

Cigarette smoking is strongly associated with an increased risk of CHD among women with type 2 diabetes mellitus. Furthermore, quitting smoking seems to decrease this excess risk substantially; women with diabetes should be strongly advised against smoking**.**

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