

The Effect of Smoking on Some Microvascular Complications in Type 2 Diabetics

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Abstract:

Background: Smoking is associated with increased risk and enhances progression of chronic diabetes related complications like nephropathy and retinopathy.

Objective: This study was designed to assess the effect of smoking on the development of some chronic diabetes related complications namely nephropathy and retinopathy.

Methods: This is a cross sectional study that enrolled 100 patients with diabetes mellitus, 50 patients were smokers and the other 50 patients were non-smokers. The patients had been randomly selected from those who had attended the National Diabetes Center-Baghdad/Iraq during the period between the 1st of January 2004, to the 1st of June 2004. All of the patients have been asked for their history of smoking by a questionnaire form and they had been examined and investigated to assess their glycaemic control and diagnosing any chronic diabetic complication that might be present. Statistical analysis had been done using Chi square test and $P < 0.05$ is considered significant.

Results: This study revealed male to female ratio of 6:1, 66% of patients were 40-59 year-old, 70% had diabetes for less than 15 years, 92% had smoked for 10 years or longer time, 60% smoked more than 1 pack (20 cigarettes) per day, the male :female ratio ,age range of patients and duration of diabetes in the non-smoker group were almost identical to smoker diabetics .84% of smoker diabetics had HbA1c level of 7.0% or more, while 64% of non-smoker diabetics had HbA1c $\geq 7.0\%$. 88% of non-smoker diabetics had abnormal BMI (being overweight, obese, and morbidly obese) compared to only 62% of smoker diabetics with abnormal BMI . 50% of smoker diabetics had positive Micral test for micro albuminuria, while only 28% of non-smoker diabetics had positive Micral test. 60% and 34% of smoker and non-smoker diabetics respectively had evidence of retinopathy in its different stages. Statistical analysis revealed significant association between being smoker diabetic and poorer glycaemic control ($P < 0.05$), occurrence of microalbuminurea ($P < 0.05$) and development of diabetic retinopathy ($P < 0.05$).

Conclusions: This study indicated that smoking significantly enhances the development of chronic diabetes related complications namely nephropathy and retinopathy. In order to reach strict or near strict glycaemic control which is the corner stone in primary as well as secondary prevention of chronic diabetes related complications, smoking cessation must be encouraged to get better and longer life for diabetics.

Introduction:

Cigarette smoking is a major cause of premature death in the world ⁽¹⁾. In 1912, it was first suggested that inhalation of cigarette smoke might be a cause of lung cancer ⁽¹⁾, since then, knowledge about the adverse health effects of smoking has accumulated.

It had been estimated that at the year 2000, 4.83 million premature deaths in the world were attributable to smoking; 2.41 million in developing countries and 2.43 million in industrialized countries, 3.84 million of these deaths were in men ⁽²⁾. The leading causes of death from smoking were cardiovascular diseases (1.69 million deaths), chronic obstructive pulmonary disease (0.97

million deaths), and lung cancer (0.85 million deaths)⁽²⁾. On the other hand, the incidence of diabetes has reached epidemic proportions across the world⁽³⁾.

Diabetes is associated with a marked increase (by two to four folds) in the risk of coronary heart disease, which can be regarded as the main cause of premature mortality among diabetics, coronary heart disease is associated with an increase in mortality among diabetics by three to seven folds⁽⁴⁾. In addition, diabetes is the leading cause of blindness in working-age adults, end-stage renal disease (ESRD), and non-traumatic lower limb amputations, furthermore, smoker diabetics have a marked increased morbidity and mortality from any cause⁽⁴⁻⁵⁾.

The prevalence of smoking among people with diabetes appears to mirror that of the general population, at least at younger ages⁽⁶⁾. In 1988, using results of the Behavioral Risk Factor Surveillance System, a cross-sectional telephone interview that assessed chronic disease risk factors in individuals across 37 states in USA, over 3000 people reporting diabetes were compared with less than 52000 without diabetes, similar percentages of smokers (26%), ex-smokers (25.9%), and those who never smoked (48.1%) were found in both populations⁽⁷⁾.

There is evidence that supports a suggested hypothesis about a causal relationship between smoking and type 2 diabetes mellitus, several prospective cohort studies suggest that smoking is associated with the development of diabetes, in the Nurses' Health Study, 114,247 women were followed for 8 years and 2,333 cases of type 2 diabetes were confirmed⁽⁸⁾. After controlling for multiple risk factors, the relative risk of type 2 diabetes among women smoking greater or equal to 25 cigarettes per day compared with individuals who never smoked was 1.42 (95%CI=1.18-1.72), suggesting a moderate association between smoking and the subsequent development of diabetes⁽⁸⁾.

After examining the effects of smoking on the 8-year incidence of type 2 diabetes on 2312 Japanese men, Kawakami *et al*⁽⁹⁾ also concluded that age of smoking initiation and number of cigarettes smoked were major risk factors for developing diabetes. This association can be related to that smokers have a much more marked insulin resistance than non smokers⁽⁹⁾.

Targher *et al* studied 40 patients with type 2 diabetes and found insulin resistance was markedly aggravated among those who smoked⁽¹⁰⁾. In addition, smoking also appears to be associated with larger upper body fat distribution, a marker of insulin resistance, raised plasma glucose concentrations, and overt diabetes⁽¹¹⁾.

Micro vascular disease (retinopathy, neuropathy and nephropathy) is an important cause for morbidity in diabetes, but diseases of the larger arteries and the heart are responsible for well over half of all deaths in diabetic patients⁽¹²⁾.

Smoking is associated with endothelial dysfunction and lipid disorders similar to those found in the insulin resistance syndrome⁽¹³⁾. Therefore, it has harmful effect on metabolic control and long term complications of diabetes, an effect that can be at least partially related to increasing components of insulin resistance syndrome⁽¹⁴⁾. By many prospective and cohort studies, it had been shown that if there is no major weight gain after smoking cessation, the latter is accompanied by a progressive return to normal insulin sensitivity⁽¹⁵⁾.

This cross sectional study had been designed to assess the effect of smoking on the development of some chronic diabetic complications namely nephropathy and retinopathy.

Patients and Methods:

This cross sectional study had enrolled 100 diabetic patients, 50 patients were smokers and the other 50 patients were non-smokers. The patients had been randomly selected from those patients attending the National Diabetes Centre in Al-mustansiriya University, Baghdad-Iraq during the period from the 1st of January to the 1st of June, 2004.

All patients had been thoroughly examined physically and had been sent for biochemical test that assess the glycemic control of diabetes namely HbA1c, and Micral test for the detection of

microalbuminuria (urine test was performed before that to ensure that there is no urinary tract infection that could affect the result of Micral test) .

All of the patients had been selected to be normotensive without any history of hypertension or receiving any antihypertensive therapy. In addition, the retina of all of the patients had been examined using direct ophthalmoscope with dilatation.

Statistical analysis had been made using chi square test to assess the significance of differences in means between smoker and non-smoker diabetics and a $P < 0.05$ was considered significant.

Result:

This study had enrolled 50 smoker diabetic patients, 7 (14%) of them were female, with a male to female ratio of about 6:1. Age of the sample ranged between 24-75 year-old (mean 51.84 ± 10.71 year). 33 (66%) patients were 40-59 year old among smokers while 56% were 40-59 years among non-smokers.

This study revealed that 37 (74%) of smoker diabetic had positive family history of diabetes, while 32 (64%) of non-smoker diabetics had family history of diabetes.

In this study, duration of diabetes mellitus ranged between 0.5-30 years (10.94 ± 8.09 years). 15 (30%) ,32(64%) of smokers and non-smokers patients respectively had diabetes for more than 15 years.

Duration of smoking in the sample included in this study ranged 3 - 50 years (21.56 ± 11.71 years). 46 (92%) patients had smoked for 10 years or longer time.

Number of cigarettes which had been smoked was 2-40 cigarettes/day (18.58 ± 15.49 cigarettes/day). 30 (60%) patients smoked more than 1 pack (20 cigarettes) per day. Figure 1 shows patients' distribution according to number of cigarettes smoked by them.

HbA1c level ranged between 4.9-18.8% in smoker diabetics ($9.33 \pm 2.48\%$), and 4.8-13.2% in non-smoker diabetics ($8.06 \pm 1.83\%$). 42 (84%) smoker diabetic patients had HbA1c level of 7.0% or more. On the other hand, 28 (64%) non-smoker diabetic patients had HbA1c level of 7.0% or more. Statistical analysis indicated a highly significant difference in HbA1c level between smoker diabetics and non-smoker diabetics ($\chi^2 = 5.197$, $P < 0.05$). Figure 2 shows HbA1c level in smoker diabetics compared to that in non-smoker diabetics.

This study indicated a range for body mass index (BMI) of 14-48 (27.54 ± 6.34) and 22-48 (30 ± 4.53) in smoker and non smoker diabetics respectively. 44 (88%) non-smoker diabetic patients had abnormal BMI i.e. being overweight, obese, and morbidly obese, compared to only 31 (62%) smoker diabetic patients with abnormal BMI (fig 3). Statistical analysis using chi square test showed a highly significant difference between smokers and non-smoker and being overweight, obese or morbidly obese , $P < 0.05$.

Regarding the development of microalbuminuria, 25 (50%) smoker diabetic patients had positive Micral test for microalbuminuria, while only 14 (28%) non smoker diabetic patients had positive Micral test (fig 4). Statistical analysis showed a significant difference in frequency of microalbuminuria between smoker and non-smoker diabetics ($\chi^2 = 5.086$, $P < 0.05$).

Thirty (60%) smoker diabetic patients had evidence of diabetic retinopathy in its different stages, while only 17 (34%) non-smoker diabetic patients had diabetic retinopathy in its different stages (fig 5). The difference in frequency of retinopathy between smoker and non-smoker diabetics was statistically significant ($\chi^2 = 6.78$, $P < 0.01$) .

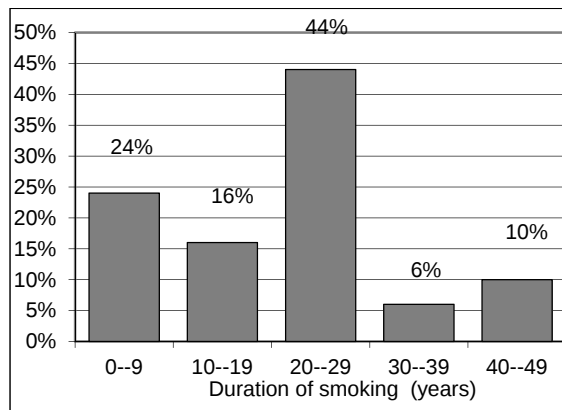


Figure 1: Patients distribution according to number of cigarettes smoked per day.

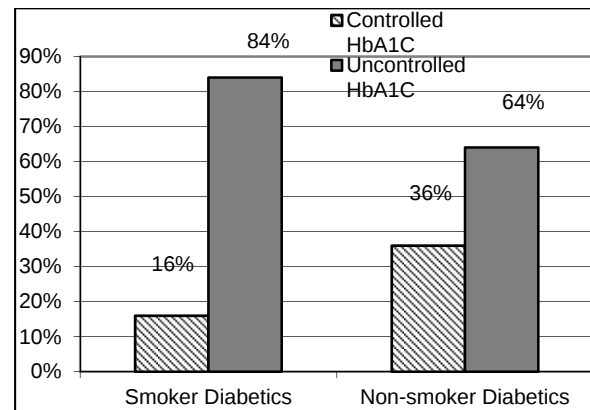


Figure 2: Hb A1C level in smoker diabetics compared to that of non-smoker diabetics.

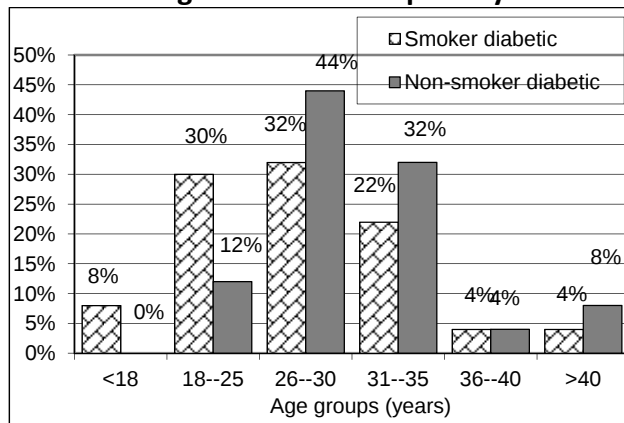


Figure 3: Patients distribution (smoker and non-smokers) according to their BMI.

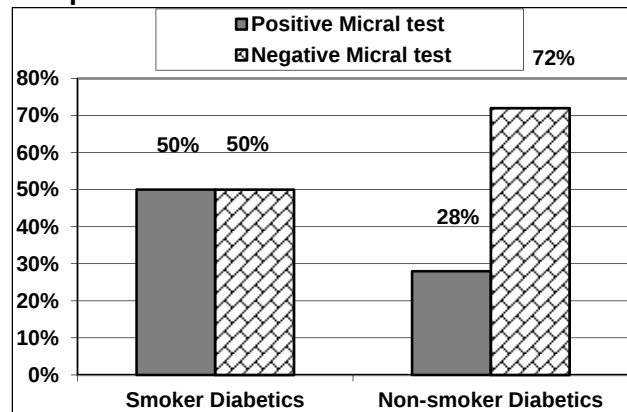


Figure 4: Frequency of microalbuminuria among smoker and non-smoker diabetics.

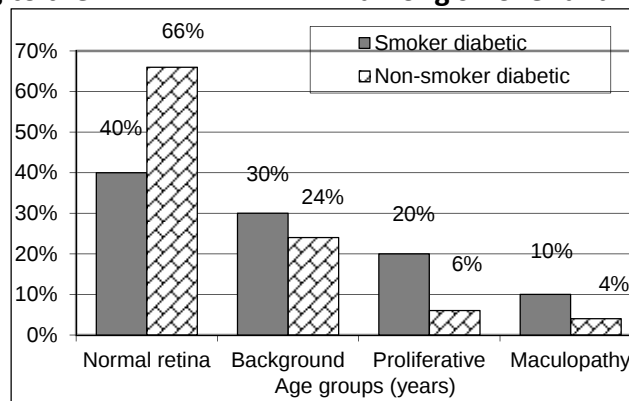


Figure 5: Frequency of different stages of retinopathy among smoker and non-smokers diabetics.

Discussion:

Regarding the relation between the duration of diabetes and the frequency of smoking this study revealed that there is an inverse relationship between smoking and duration of diabetes, only 30% of smoker diabetics who had been enrolled in this study had diabetes for more than 15 years. This finding can be explained in part by the increased mortality associated with the combination of smoking and diabetes.

In addition to the duration of smoking, the other important risk factor for increasing the risk of developing smoking associated complications and death is the number of cigarette smoked per day⁽¹⁶⁾. Unfortunately in this study, 60% of smoker diabetics had smoked more than 1 pack (20 cigarettes) per day. There are positive and significant dose response relationships between

measures of cigarette smoking (including cigarettes per day, duration of smoking) and increased risk of the ordinary as well as the novel risk factors for cardiovascular disease⁽¹⁷⁾.

On the other hand, the other important marker for glycemic control which is the glycated hemoglobin (HbA1c) was 7% or more in 84% and 64% of smoker diabetics and non-smoker diabetics that included in this study respectively. This finding is in agreement with the results of many other cohort and prospective studies^(10,15). Smoking is associated with increased plasma glucose and therefore elevated HbA1C, because it enhances insulin resistance and is associated with increased risk of truncal obesity, a marker of insulin resistance. It had been found also that hormonal responses are significantly higher in smoker diabetics, specifically growth hormone, arginine vasopressin, and cortisol responses⁽¹⁰⁾, which could make smokers more liable for uncontrolled blood glucose level. Bott *et al*, as part of a large prospective multicentre study with 697 type 1 diabetic subjects, concluded that smoking was one of the strongest predictors of poor metabolic control revealing less than 20% frequency of accepted glycemic control⁽¹⁸⁾.

Smoking is related to the premature development of multiple complications of diabetes^(19,20). Nephropathy has been reported as common complication in type 1 diabetic patients who smoke, and smoking increases the risk for microalbuminuria in type 2 diabetes⁽²⁰⁻²¹⁾. This study indicated a highly significant association between smoking and the development of microalbuminuria ($\chi^2=5.086$, $P<0.02$), positive Micral test was about 2 times more frequent among smoker diabetic (50% of smoker diabetics, 28% in non smoker diabetics) (fig 4). Several studies have documented the relationship of smoking to the development of nephropathy in type 1 and type 2 diabetes. Chase *et al*⁽²²⁾ conducted a longitudinal study of 359 type 1 diabetic patients. When compared to non-smokers, smokers were 2.2 times at greater risk for albuminuria⁽²²⁾. Sawicki *et al*⁽²³⁾ also found that progression of nephropathy was significantly less common among non-smokers (11%) than smokers (53%) or those who had quit smoking (33%)⁽²³⁾. Ikeda *et al*, conducted a cross sectional study of 148 men with type 2 diabetes mellitus, concluding that the incidence of micro- and macroalbuminuria were significantly higher in current smokers (53%) compared with ex-smoker (33%) and non-smoker (20%)⁽²⁴⁾. The reason why albuminuria is more prevalent in diabetic smoker than in non-smoker is probably due to increased incidence of metabolic syndrome among smokers which is a risk factor for low glomerular filtration rate (GFR) and therefore impaired renal function⁽²⁵⁾, another possible explanation is that smokers have a heightened state of oxidative stress, which is likely to play a role in inducing vascular and endothelial dysfunction, a mechanism that might be involved in increased risk of deteriorating renal function⁽²⁶⁾. The relationship of cigarette smoking to retinopathy is less well defined than that with other microvascular complications of diabetes. This study revealed a significant relationship between smoking and the development of diabetic retinopathy in its different stages ($\chi^2=6.78$, $P<0.01$), the frequency of diabetic retinopathy among smoker diabetics who had been included in this study was 60%, compared to 34% of non-smoker diabetics. As reported by Klein *et al*⁽²⁷⁾, most epidemiological research has not found a positive relationship between smoking and retinopathy although there have been studies that have suggested such a relationship⁽²⁸⁾. The higher incidence of retinopathy in smoker diabetics may be due to the fact that smoking reduces retinal blood flow and potentiates the hypoxic environment of the diabetic retina and so will be more prone for retinopathy⁽²⁹⁾. Reichard found significant relationship between smoking and the progression of micro vascular complications in 96 type 1 diabetic patients, followed over 5 years, progression of retinopathy was independently related to smoking habit⁽³⁰⁾. As part of multicentre prospective study, Mulhauser *et al* also concluded that there were significant relationships between smoking, retinopathy, and nephropathy⁽²⁰⁾. So in conclusion this study showed that retinopathy occurs more commonly in smoker diabetic patients than the non-smokers. Also nephropathy and microalbuminuria does seem to be affected significantly by smoking. So smoking cessation advice should be a routine component of diabetic care by identifying triggers to smoking and encourage

smokers to develop strategies for countering them and by combating psychological and physical nicotine addiction when it is appropriate.

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