Cigarette Smoking and Diabetic Retinopathy

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SUMMARY

A sample of 181 diabetics with diabetic retinopathy was statistically investigated with regard to association of smoking with proliferative retinopathy. The numbers of patients with proliferative retinopathy rose with increasing tobacco consumption. In nonsmokers no association existed between diabetes duration and proliferative retinopathy, but in smokers the number with proliferative retinopathy rose with increasing diabetes duration. DIABETES *26*:46-49, **January, 1977.**

Four factors are associated with diabetic retinopathy: the quality of diabetic control,[1] the duration of disease, age at diabetes onset, and age of the patient.[2] The aim of this research was to investigate smoking as an additional factor. The investigation was prompted by a clinical observation that many diabetics with proliferative retinopathy were heavy smokers and that a number of long-duration diabetics who had minimal retinopathy were nonsmokers. This led to the postulate that smoking may be related to the deterioration of diabetic retinopathy from the simple background type to the proliferative state. To test this hypothesis, clinical records of nonsmoking and smoking diabetics with retinopathy were analyzed for occurrence of nonproliferative and proliferative retinopathy.

METHOD

A clinical history was collected on 181 diabetics who had attended the University of Alberta Fluorescein Angiography Unit consecutively during a 21-month period. The sample contained 97 patients with nonproliferative and 84 with proliferative retinopathy. There were 85 males and 96 females, their distribution showing a slight excess of female nonsmokers in the older groups and of female smokers in the youngest groups.

The patients were referred at the discretion of their ophthalmologists for diagnostic service in the unit, the only such facility serving a population of one million.

A cigarette smoker was considered to be a person who was regularly smoking one or more cigarettes per day at the time of the interview or within seven years of the study. A nonsmoker was a person who had not smoked at all in eight years prior to the study. Pipe and cigar smokers and people heavily exposed to smoke in the environment[3] were excluded. Those excluded as passive smokers consistently spent several hours a day in the company of heavy smokers in either the home or office. Many volunteered a history of eye irritation from the smoke.

The concept of "pack years" was used to provide a quantitation of exposure to tobacco over the duration of diabetes. A person who smoked one pack of 20 cigarettes per day for one year was considered to have accumulated one pack year. When tobacco consumption was irregular, the varying consumption was prorated in order to calculate total pack years. Smoking prior to diagnosis of diabetes was not considered.

The duration of diabetes was considered to be the time from first diagnosis until last attendance in the unit. Duration of proliferative retinopathy could not be determined because of uncertainty about its time of onset. Any patient whose angiogram showed an area

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of fluorescein leak characteristic of neovascularization was considered to have proliferative and all others nonproliferative disease. Retinopathy leads to visual loss by two pathways: the complications of proliferation including hemorrhage and detachment and the complications of an exudative process at the macula seen mainly in adult-onset diabetics. Loss of vision from lipoid macular deposits can occur in eyes free of proliferation. All patients referred because of visual loss of 20/50 or less with associated macular lipoid deposits were treated separately. Only then could it be assumed that the nonproliferative group contained patients with a milder form of retinopathy than the proliferative group.

RESULTS

Data were analyzed by the chi-square test. Lipoid plaques were found at the macula of 30 adult-onset and one juvenile-onset diabetics. Of the 31 patients, only six (19 per cent) were cigarette smokers.

TABLE 1

Distribution by age and tobacco in sample of diabetics with retinopathy

	Age of diabetics (years)			
Tobacco	15-29	30-44	45-59	60+
Nonsmokers	6	18	24	20
Smokers	31	20	21	10

TABLE 2

Prevalence in smoking diabetics of nonproliferative and proliferative retinopathy in relation to tobacco consumption

	Tobacco consumption (pack years)			
Retinopathy	1/2-4	5-9	10-14	15+
Nonproliferative	21	11	7	2
Proliferative	8	14	11	8

TABLE 3

Prevalence in nonsmoking and smoking diabetics of nonproliferative and proliferative retinopathy in relation to duration of diabetes

	Diabetes duration in years			
	Nonsmokers			
Retinopathy	1–9	10–19	20–29	30+
Nonproliferative	4	17	16	2
Proliferative	2	11	12	4
	Smokers			
Retinopathy	1–9	10–19	20–29	30+
Nonproliferative	12	23	6	0
Proliferative	2	14	17	8

The remaining 150 patients, who were free of lipoid maculopathy, are presented in table 1 by age and smoking habit. Analysis reveals that the age of the diabetics is related to whether or not they smoked, younger diabetics having been more likely than older ones to have been smokers ($X^2 = 32.6$, $p < 0.001$).

Distribution of patients with nonproliferative and proliferative retinopathy in relation to tobacco consumption in pack years is shown in table 2. A significant trend exists ($X^2 = 10.6$, $p < 0.02$) for the number of patients with proliferative retinopathy to increase with tobacco consumption.

Table 3 presents the distribution of nonsmoking patients with nonproliferative and proliferative retinopathy in relation to duration of diabetes. No relationship ($X^2 = 2.82$, N.S.) exists between duration and the proliferative status of the patient. This table also presents data for smokers. In contrast to the nonsmokers, there is a significant tendency for the proportion of smoking patients with proliferative retinopathy to increase with diabetes duration ($X^2 = 20.21$, $p < 0.001$).

Table 4 presents the distribution of patients with nonproliferative and proliferative retinopathy in relation to smoking status in two duration groups, those with diabetes less than 20 years and those with 20 years and more. In the shorter-duration group there was no association ($X^2 = 0.25$, N.S.) between smoking and degree of retinopathy. In the long-duration group smoking was significantly related ($X^2 = 6.1$, $p < 0.02$) to the number of patients with proliferative retinopathy.

Table 5 presents the relationship of proliferation to age. No significant associations were found either in the nonsmokers ($X^2 = 3.97$, N.S.) or in the smokers ($X^2 = 2.00$, N.S.).

A similar analysis is shown in table 6 with respect

TABLE 4

Prevalence of proliferative retinopathy in relation to nonsmoking and smoking in patients with diabetes duration less than 20 years and duration 20 years and more

		Diabetes duration less than 20 years
Retinopathy	Nonsmokers	Smokers
Nonproliferative	21	35
Proliferative	13	16
		Diabetes duration 20 years and more
Retinopathy	Nonsmokers	Smokers
Nonproliferative	18	6
Proliferative	16	25

TABLE 5

Prevalence of proliferative retinopathy in relation to age

	Current age of diabetics			
	15–29	30–44	45–59	60+
	Nonsmokers			
Nonproliferative	3	7	16	13
Proliferative	3	11	8	7
	Smokers			
Nonproliferative	18	10	8	5
Proliferative	13	10	13	5

TABLE 6

Prevalence of proliferative retinopathy in relation to age at onset of diabetes

	Diabetes onset age in years			
	0–19	20–39	40–59	60+
	Nonsmokers			
Nonproliferative	7	16	14	2
Proliferative	13	9	7	0
	Smokers			
Nonproliferative	23	8	8	2
Proliferative	28	7	6	0

to age at diabetes onset, and again no significant association was found in the nonsmokers ($X^2 = 6.77$, N.S.) or in the smokers ($X^2 = 2.84$, N.S.).

DISCUSSION

Both diabetics[5] and smokers[6] are prone to develop cardiovascular disease; thus the combination of smoking and diabetes may aggravate retinopathy.

The information available in the unit was not adequate to evaluate control in relation to smoking. Therefore it was assumed that a spread of good to poor control existed equally among smokers and nonsmokers. The interaction of control and smoking should be studied in the future.

No evidence was found that smoking contributes to lipoid maculopathy. In patients without maculopathy it is assumed that a change from nonproliferative to proliferative retinopathy presents an increase in severity of eye disease. If low tobacco consumption is associated with a limited number of patients with proliferative retinopathy and high consumption with many more patients, smoking may be a contributory factor in the development of proliferation. The data in table 2 support this hypothesis by demonstrating that increasing tobacco consumption is significantly associated with those patients with proliferation.

It might be argued that the increasing pack years may not be an indication that retinopathy is related to tobacco but rather that retinopathy is related to duration of disease. If tobacco consumption is not a factor that affects retinopathy we should find that the proportion of patients with proliferative retinopathy should increase with diabetes duration for both smoking and nonsmoking diabetics. But our findings showed that duration of disease did not increase the likelihood of developing proliferative retinopathy in nonsmokers, while it did in smokers.

If both duration of diabetes and duration of tobacco exposure are associated with retinopathy we should find a stronger association between smoking and proliferative retinopathy in the long-duration group than in the short-duration group. Indeed, the longer-duration group showed that proliferative retinopathy was significantly associated with smoking, while in the shorter-duration group there was no relationship. This suggests that deterioration from nonproliferative to proliferative retinopathy is a function of the combination of duration and exposure to tobacco.

If current age and age at diabetes onset are associated with retinopathy severity, confounding by age could have explained our results (since age is related to smoking). However, there was no association between age and the degree of retinopathy.

The finding that the severity of retinopathy is statistically associated with smoking and not with duration, current age, or onset age, suggests a cause-and-effect relationship. This conclusion is supported by a study at the Joslin Clinic of juvenile diabetics surviving 40 years of disease.[7] Eighty-seven per cent of 73 patients had retained useful vision in spite of long duration. The authors suggest that good control may have been a factor in the freedom from complications. While they do not mention tobacco, it has been stated by the Joslin Clinic[8] that "careful control of diabetes with omission of smoking in all cases are points to be reëmphasized." The combination of good control and nonsmoking may have contributed to the low ocular complication rate. Further study must be done to determine the psychologic reasons for diabetics' smoking, especially in the young patient. The cigarette may be used as a tool for limiting food consumption or it may reflect the anxiety concerning complications of the disease.

Several authors have suggested an association between proliferative retinopathy and hypoxia.[10,11] Heavy smokers were found to have carboxyhemoglobin levels as high as 15 per cent.[12] Chronic exposure to low levels of carbon monoxide may further embarrass tissue oxygen supply in disease states where ox-

ygen delivery to tissue is already marginal.[13] The reduplication of the capillary basal lamina seen in diabetics with retinopathy[14] relates to an accelerated cell death rate and possibly an unusual susceptibility to ordinary levels of injury.[15] Carbon-monoxide-induced hypoxia could be a toxic stimulus to the retinal vasculature.

It is suggested from both animal and human studies that carbon monoxide causes a separation of arterial endothelial cells and thus causes edema.[16,17] Such an effect could aggravate retinopathy. Patients with retinopathy were found to have an increased tendency to platelet aggregation.[18] This could be due to nicotine, which is known to increase platelet stickiness.[19]

If our findings are confirmed, the practical clinical recommendation is that diabetics be strongly urged to avoid tobacco.

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