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Alcohol Consumption, but Not Physical Activity or Smoking, Contribute To Advanced Forms of Diabetic Retinopathy: A Case-Control Study

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Abstract

Background: Modifiable risk factors, like dyslipidemia and lifestyle factors such as smoking, alcohol use and physical activity, may have an impact in the prevention of diabetic retinopathy despite diabetes control and duration. Previous studies on the significance of alcohol consumption, physical activity/exercise and smoking, however, in diabetic retinopathy are conflicting. We investigated these lifestyle factors and their mutual interaction in diabetic retinopathy.

Methods: This study is an observational, retrospective case-control study. The diabetic retinopathy group (DR) consisted of 182 patients with type 1 or type 2 diabetes and proliferative diabetic retinopathy or maculopathy. The patients were either laser-treated and/or had undergone vitrectomy. The control (DC) group comprised of 98 diabetic patients (type 1 or type 2) attending screening for diabetic retinopathy. They had very mild background or no retinopathy and their diabetes duration was at least 10 years.

Results: The DC group was more physically active than DR, since 43% of DC group reported long-lasting regular physical activity compared with 25% in DR, respectively (p=0.001 (χ^2)). In DR group, the amount of physical activity was inversely correlated with diabetic neuropathy (R= -0,159, p= 0.037), but not with diabetic nephropathy (R= -0.139, p= 0.66). Fifty percent of the DR group and 66 % of the DC group consumed alcohol occasionally with abstinence being reported by 42% of the patients in DR group and 23% in DC group (p was 0.017 (χ^2)). Smoking habits did not differ significantly between the DR and DC groups. In multivariate logistic regression analysis, only alcohol consumption had significant association with DR (OR 0.331, 95% CI 0.147-0.748, p=0.008 for occasional alcohol consumption and OR 0.148, 95% CI 0.038-0.577, p=0.006 for regular alcohol consumption).

Conclusions: Alcohol consumption seems to contribute to advanced forms of diabetic retinopathy. Although patients with DR are physically less active than DC, physical activity is not significantly associated with DR probably due to its correlation with neuropathy.

Keywords: Exercise; Diabetes; Diabetes complication; Smoking; Ethanol

Introduction

The well-known risk factors for the development of diabetic retinopathy are the duration of diabetes and diabetes control. Diabetes control plays a key role in the prevention of diabetic retinopathy [1] and it is known to influence the incidence and progress of diabetic retinopathy independent of age, diabetes type, diabetes duration and the severity of retinopathy [2,3]. Other modifiable risk factors, e.g. blood pressure, dyslipidemia and lifestyle factors such as smoking, alcohol use and physical activity, may also have a major impact in preventing diabetic retinopathy.

There is some evidence that physical activity or exercise can have a protective impact against diabetic retinopathy. Physical activity has been shown to be protective or at least not promote development of diabetic retinopathy in type 1 diabetes [4]. In addition, work-related physical activity seems to confer some protection against the risk of diabetic retinopathy (OR 0.66, 95 % CI 0.51–0.85) as shown in the recent study by Tikellis et al. [5]. In the FinnDiane study, low-intensity physical activity was independently associated with an increased risk of proliferative retinopathy (OR 1.49, 95 % CI 1.15–1.93), but there was no association with the frequency of activity [6]. However, in some studies, the exercise level did not correlate with the progression of diabetic retinopathy [7] or proliferative diabetic retinopathy [8].

The scanty information that exists on the association between alcohol and diabetic retinopathy is inconsistent. In a five-year prospective study, the risk of suffering any severity of diabetic retinopathy was significantly increased with daily alcohol consumption of 30 g or more (RR 2.25, 95% CI 1.15-4.42) [9]. In WESDR-study [10] a cross sectional- study revealed that moderate alcohol use decreased the prevalence of diabetic retinopathy in type 1 diabetics (OR 0.49, 95% CI 0.27-0.92), but in prospective population-based studies no such association was found [11,12]. In a recent study, moderate consumption of alcohol was not associated with either the presence (OR 0.91, 95% CI 0.62- 1.35) or progression (OR 0.84, 95% CI 0.46-1.55) of diabetic retinopathy in patients with type 2 diabetes [13]. Furthermore, the study by Giuffre et al. observed no association in their multivariate model (OR 0.43, 95% CI 0.11–1.67 for alcohol consumption under 20 years),

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whereas Beulens reported a protective effect of alcohol against any type of diabetic retinopathy [14,15] and moderate consumers had the lowest risk (OR 0.60, 95% CI 0.37–0.99) for proliferative retinopathy.

The literature reports on smoking as a risk factor for diabetic retinopathy indicate weak or no association. In the study by Moss et al. [16] pack-years were correlated with the risk of incidence of proliferative diabetic retinopathy in patients with older-onset diabetes requiring insulin, but it was not thought likely to be an independent risk factor for diabetic retinopathy (p=0.052 after controlling for known risk factors for diabetic retinopathy) [16]. In their cohort study, smoking status or pack-years were not associated with the incidence or progression of diabetic retinopathy or progression of proliferative retinopathy [17]. However, a significant association between diabetic retinopathy and smoking has been detected in German cohort studies (OR 1.3, 95% CI 1.13-1.48, p=0.0002 in a study by Hammes for any retinopathy and OR 1.44, 95% CI 1.10-1.88, p=0.0075 in study by Muhlhauser for retinopathy and pack years) [18,19] and in DCCT study (R= 0.09, *P* <0 .001) [7]. Furthermore, in the UKPDS study, the incidence and development of diabetic retinopathy were associated with non-smoking status (OR 0.63, 95% CI 0.48-0.82) [20].

The current study aimed at evaluating the significance of three life-style factors i.e. alcohol consumption, physical exercise and smoking on diabetic retinopathy. The information on the significance of these lifestyle factors is somewhat inconsistent and they may undergo mutual interactions.

Methods

This study is an observational, retrospective case-control study. The diabetic retinopathy group (DR) consisted of patients with type 1 or type 2 diabetes having proliferative diabetic retinopathy or maculopathy who were treated in the Department of Ophthalmology, Oulu University Hospital. The patients were either laser-treated and/or vitrectomy had been performed. Recruited diabetic control (DC) group included diabetic patients (type 1 or type 2) attending fundus imaging for screening of diabetic retinopathy in Oulu City Health Centres. The diagnosis and grading of diabetic retinopathy were conducted by an expert ophthalmologist from 60 degree fundus photographs through dilated pupils and by clinical examination. The patients were matched for diabetes duration by including patients with diabetes duration of at least 10 years in the DC group. Only patients with no retinopathy or at most a few micro aneurysms were included in the DC group.

In both the DR and DC groups, basic blood tests (e.g. fasting blood glucose level, glycated haemoglobin, creatinine, CRP) as well as determinations of plasma lipids and lipid metabolism were performed. All subjects were interviewed about their health status (e.g. type of diabetes, duration of diabetes, micro- and macro vascular diabetes complications, hypertension and medications). Smoking status, alcohol use and exercise habits were enquired in a questionnaire. Smoking status was classified as smoker, ex-smoker or non-smoker and the amount of cigarettes per day were recorded as well as total duration of smoking in years. Pack-years were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Physical activity was designated as no activity, occasional activity (occasional walking, gardening etc.), regular activity (1-2 times/week) or long-lasting regular activity (at least 30 min at least three times/week). Alcohol consumption was subdivided into four classes, i.e. no consumption, occasional consumption (less than once/week), regular (more than once/week), or daily alcohol consumption.

A total of 313 consecutive diabetic patients were recruited in and 280 diabetic completed the questionnaire and provided blood samples. The diabetic retinopathy (DR) group consisted of 182 diabetics with diabetic retinopathy (maculopathy or proliferative retinopathy) and the diabetic control (DC) group of 98 diabetic controls without retinopathy or with very mild background retinopathy (only a few micro aneurysms).

Participation in the study was voluntary and all subjects had the right to revoke their permission without affecting their future treatment. Patient data were collected from the medical records of the Oulu University Hospital and Oulu City Health Centres. This study was approved by the Ethics Committee of the Oulu University Hospital and all the study subjects provided written informed consent.

Statistical analyses

The statistical analyses were carried out using SPSS Statistics software version 19.0 (SPSS, Inc., Chicago, IL, USA). The differences between the means were assessed by independent Student's t test or Mann-Whitney test after checking the data for a normal distribution. For dichotomous variables, χ^2 test was used. We used Pearson correlation coefficient (two-tailed) to investigate the relation between physical activity, hypertension and diabetes complications, as well as smoking and alcohol consumption. Logistic regression analysis was used to explain the risk for diabetic retinopathy, and those variables displaying a significant difference between DC and DR groups were included in the model (BMI, HDL cholesterol, triglycerides, glycated haemoglobin). Smoking, physical activity and alcohol consumption were included as well as hypertension, diabetic nephropathy and neuropathy, since they had correlation with smoking and physical activity. The model was comprised using factors known to correlate with diabetic retinopathy as mentioned above. The criteria for statistical significance were p values less than 0.05.

Results

Clinical characteristics

The clinical characteristics of the study subjects are shown in Table 1. The groups were comparable in terms of sex distribution, age and diabetes duration and diabetes type. The percentage of patients with systemic hypertension (antihypertensive medication or hypertensive without medication) was 76% vs. 52% of the DR and DC group, respectively (p=0.000 (χ^2).The DR group had significantly higher glycated haemoglobin (p=0.000, t test) and their body mass index was higher than in the DC group (0.018, t test) (Table 1). Fasting plasma cholesterol and HDL cholesterol did not differ significantly between DR and DC groups, but the DR group had a higher plasma triglyceride concentration and a lower HDL concentration than the DC group (Table 2).

Physical activity

The DC group was more active than subjects in DR, since 43% of the DC group but only 25 % of the DR group reported long-lasting regular physical activity. Conversely, 11 % of the DR group, but only 1 % of the DC group were physically inactive (Figure 1) (p=0.001 (χ^2). Physical activity differed also between diabetes types, i.e. 50 %

of the type 1 diabetics in DC group and 35 % of type 2 diabetics in DC group reported taking regular long-standing physical activity, while for occasional physical activity the numbers were reversed, the proportions being 21 % for type 1 and 38 % for type 2 in DC group (p 0.008 (χ^2). In DR group, physical activity was inversely correlated with the presence of diabetic neuropathy (R= -0.159, p= 0.037), but not with diabetic nephropathy (R= -0.139, p= 0.66). No such correlations were found in DC group (R=0.021, p= 0.84 for diabetic nephropathy and R=0.087, p= 0.41 for diabetic neuropathy). However, there was no correlation between the physical activity and hypertension (R= -0.122, p= 0.105 for DR and R= -0.135, p=0.105 for DC).

Alcohol consumption

The alcohol consumption in the DR and DC groups is shown in Figure 2. Every second member of the DR group (50%) and two out of every three of the DC group (66 %) consumed alcohol occasionally, but only one subject in the DR group reported daily alcohol consumption. No cases of daily alcohol consumption were reported in the DC group. Abstinence was reported by 42% of the patients in the DR group and 23% in the DC group. p was 0.017 for alcohol consumption (χ^2). There were no significant differences in alcohol consumption between diabetes type or between treatment groups (laser or vitrectomy) (p= 0.061, χ^2). Alcohol consumption correlated with smoking (R=0.296, p= 0.000) in the DR group, but not in the DC group (R=0.199, p= 0.054).

Smoking

The smoking habits did not differ significantly between the DR and DC groups. The proportion of current smokers was 21% in the DR group and 16% in the DC group (p 0.239, χ^2 test) (Figure 3) and the proportion of smokers did not differ significantly between diabetes type or in treatment groups (laser or vitrectomy) (p=0.638, χ^2 test). Smoking was also recorded as a continuous variable, since pack-years were calculated. However, pack-years did not differ between the DR and DC groups (10.9 vs. 10.2 for DR and DC, respectively, p = 0.678, Mann-Whitney). Smoking correlated with alcohol consumption (R=0.296, p= 0.000) and nephropathy (0.208, p= 0.005) in the DR group, but not in the DC group (R=0.199, p=0.054 for alcohol consumption and R=-0.005 and p=0.960 for diabetic nephropathy).

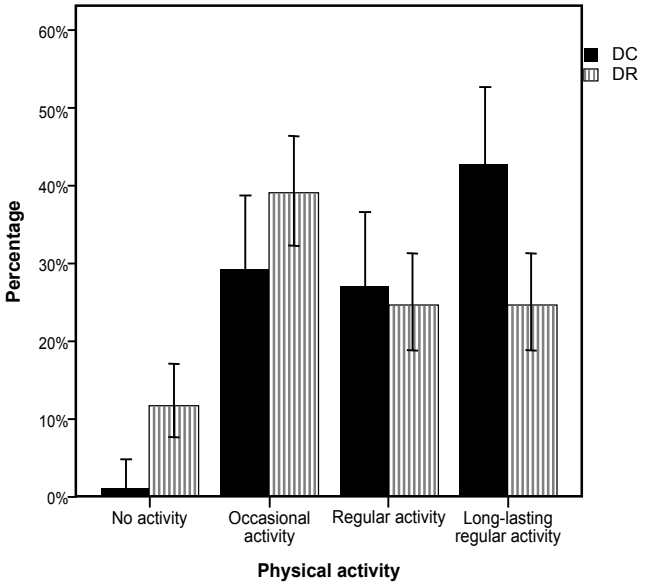

Figure 1: Physical activity in diabetic retinopathy (DR) and diabetic control (DC) groups. The data are presented as percentages and 95% confidence intervals.

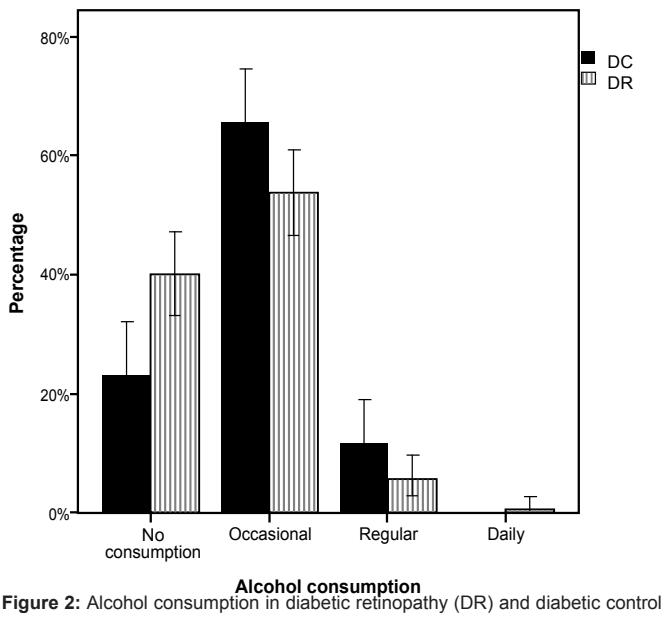

Figure 2: Alcohol consumption in diabetic retinopathy (DR) and diabetic control (DC) groups. The data are presented as percentages and 95% confidence intervals.

	Diabetic retinopathy	Diabetic controls	P
Number of patients	182	98	
Female (n (%))	78 (43 %)	48 (49 %)	0.326 (χ^2)
Male (n (%))	104 (57 %)	50 (51 %)	
Age (years)	59.2 (SD 13.8)	56.1 (SD 16.4)	0.114 (t test)
Type 1 diabetes (n (%))	85 (47 %)	48 (49 %)	0.716 (χ^2)
Type 2 diabetes (n (%))	97 (53 %)	50 (51 %)	
Maculopathy	62 (34 %)	NA	
Proliferative retinopathy	118 (65 %)	NA	
Diabetes duration (years)	23.9 (SD 10.8)	24.7 (SD 7.3)	0.503 (t test)
Glycated haemoglobin (%)	9.0 (SD 1.9)	8.3 (SD 1.3)	0.000 (t test)
Body mass index (kg/m^2)	28.8 (SD 5.7)	27.1 (SD 5.1)	0.018 (t test)
Hypertensive	139 (76%)	51 (52%)	0.000 (χ^2)
Normotensive	42 (23%)	47 (48%)	

Table 1: Clinical characteristics of the study subjects.

	Diabetic retinopathy	Diabetic controls	P (t test)
Plasma cholesterol (mmol/l)	4.5 (SD 1.1)	4.6 (SD 0.9)	0.690
LDL cholesterol (mmol/l)	2.7 (SD 0.9)	2.6 (SD 0.7)	0.259
HDL cholesterol (mmol/l)	1.3 (SD 0.3)	1.5 (SD 0.5)	0.000
Triglycerides (mmol/l)	1.7 (SD 1.3)	1.1 (SD 0.7)	0.000

Table 2: Fasting plasma lipids. The data are expressed as mean (SD).

Logistic regression

We selected variables which displayed significant difference between the DR and DC groups for inclusion in the logistic regression analysis (BMI, HDL cholesterol, triglycerides, glycated haemoglobin). Smoking, physical activity and alcohol consumption were included as well as diabetic nephropathy and neuropathy, since they had correlation with smoking and physical activity. We also included hypertension in

the model, since it might interfere with association between physical activity and diabetic retinopathy. BMI and triglycerides were not associated with the risk of diabetic retinopathy. The most impressive association was with alcohol consumption (OR 0.331, 95% CI 0.147-0.748, p=0.008 for occasional alcohol consumption and OR 0.148, 95% CI 0.038-0.577, p=0.006 for regular alcohol consumption). Occasional, regular or long-lasting regular physical activities were not significantly associated with diabetic retinopathy. Furthermore, smoking status was not associated with diabetic retinopathy in logistic regression analysis (OR 1.306, 95% CI 0.494-3.459, p=0.590 for current smoking). The results are shown in Table 3.

Discussion

The current study highlights the role of physical activity as well as alcohol consumption and smoking on diabetic retinopathy and examines their interaction. We found that alcohol consumption, but not physical activity or smoking, may contribute to advanced forms of diabetic retinopathy, although hypertension and co-morbidity in diabetic neuropathy may interfere with the interpretation of the results.

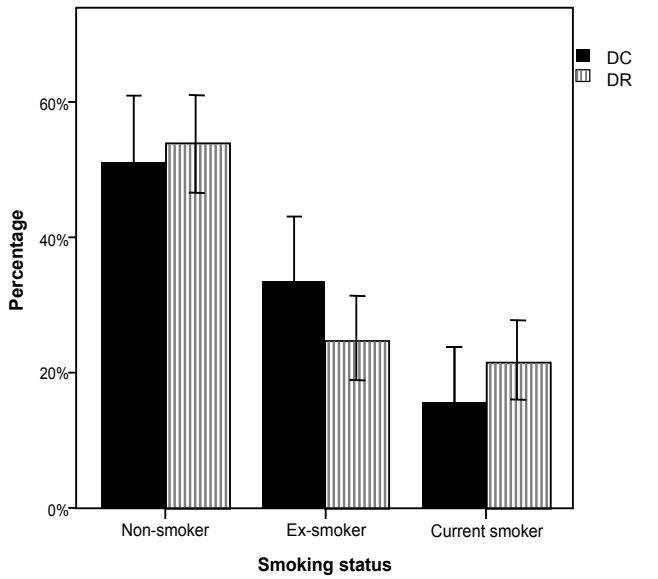

Figure 3: Smoking habits in diabetic retinopathy (DR) and diabetic control (DC) groups. The data are presented as percentages and 95% confidence intervals.

	Odds ratio	95 % confidence interval	P
Body mass index	0.963	0.895-1.036	0.313
HDL cholesterol	0.221	0.080-0.609	0.004
Triglycerides	1.568	1.024-2.4	0.038
Glycated haemoglobin	1.422	1.141-1.773	0.002
Hypertension	2.547	1.202-5.4	0.015
Diabetic nephropathy	2.119	0.891-5.037	0.089
Diabetic neuropathy	2.628	1.178-5.864	0.018
Occasional alcohol consumption	0.331	0.147-0.748	0.008
Regular alcohol consumption	0.148	0.038-0.577	0.006
Ex-smoker	0.587	0.257-1.342	0.207
Current smoker	1.306	0.494-3.459	0.590
Occasional physical activity	0.139	0.015-1.322	0.086
Regular physical activity	0.141	0.015-1.364	0.091
Long-lasting regular physical activity	0.136	0.014-1.287	0.082

Pseudo R square (Nagelkerke) was 0.366.

Table 3: Logistic regression analysis on the variables affecting the risk of diabetic retinopathy.

The benefits of physical activity on many factors, such as blood pressure, lipids and BMI are clear and known to be involved in reducing mortality in diabetic patients, even though the influence of physical activity on diabetic retinopathy has not been fully clarified [21]. Literature reports regarding the effect of physical activity on DR seem to vary depending on the study population, its setting and the determination of what constitutes physical activity/exercise, and therefore, the association may not be very strong. There are few studies examining potential benefits of active exercise on diabetic retinopathy, but there are some reports on the advantages of leisure-time physical activity as well [4]. In addition, work-related physical activity seems to confer 34 % reduced risk of having diabetic retinopathy [5]. Furthermore, despite lack of association with the frequency of physical activity, low-intensity physical activity was associated with an increased risk of proliferative retinopathy (OR 1.49, 95 % CI 1.15–1.93) [6]. Overall, the proportion of individuals actively exercising in the DC group was high in this study, since 43% of them reported long-standing regular physical activity, whereas only 25% in the DR group actively exercised. However, in logistic regression no association between diabetic retinopathy and physical activity was found in current study, and this was mainly due to correlation of neuropathy with physical activity in patients with DR. Furthermore, the lack of association may also be related to connection between hypertension and physical exercise. There is a need for a prospective study to clarify the effects of active exercise on the development of diabetic retinopathy and on prevention of morbidity of other microvascular diabetes complications.

Several studies have been conducted on the influence of alcohol consumption on diabetic retinopathy, but still there is no convincing conclusion. In the study by Young (1984), a positive association was found [9], but in most of the studies (both cross-sectional and longitudinal) the association has been absent [11,12,14,22]. However, there are also reports of a negative association [10] which is in agreement with in current study, as we found that alcohol consumption contributed to decreased risk of diabetic retinopathy. Giuffre et al. [14] found a decreased risk of diabetic retinopathy with prolonged duration of alcohol consumption, but in their multivariate model, alcohol consumption was not an independent risk factor. This apparent discrepancy may be due to differences in the study design i.e. some of the studies were cross-sectional and others longitudinal. Some studies, such as Xu et al. [12] and Giuffre et al. [14] are based on prevalence or duration of alcohol consumption while others report amounts of absolute alcohol consumed [13,15]. However, the classification of amount of alcohol consumption between studies varied considerably, and in most of them including current study, the type of alcohol being consumed has not been taken into account. Furthermore, along with the type of alcohol consumed the information over the frequency of alcohol consumption is important and should be taken into account in future studies.

The association of alcohol and diabetic retinopathy does not seem to be straight-forward, since there is evidence for a U-shaped curve in the relationship between alcohol consumption and proliferative diabetic retinopathy [15], i.e. moderate drinkers are at a lower risk (OR 0.60, 95% CI 0.37–0.99) compared with heavy drinkers or abstainers

with the association being most significant in wine drinkers. In a study by Lee et al. [14], the deteoriation of vision in diabetics was stronger in consumers of beer and spirits than wine. The possible beneficial influence of wine on diabetic retinopathy may be related to other ingredients of wine than alcohol, such as flavonoids and other polyphenols etc. that affect lipid oxidation. Besides the type of beverage consumed, the influence of alcohol consumption on the risk of diabetic retinopathy could be moderated through several mechanisms including the ability of alcohol consumption to increase plasma HDL cholesterol [10,23] even though adjustment for HDL did not affect the association of alcohol with retinopathy [15]. Furthermore, reduced platelet aggregation and especially the U-shaped association of alcohol with the plasma fibrinogen concentration [24] highlight the importance of several vascular factors which also influence diabetic retinopathy [10].

The effect of smoking on diabetic retinopathy might be associated with its harmful influence on microvascular complications in a similar manner that it influences macrovascular disease. In concert with the current study no association has been found between the incidence or progression of diabetic retinopathy and smoking in cross-sectional and cohort studies [16,17]. However, the association of smoking with diabetic retinopathy found in two cohort studies does reveal a discrepancy, which might in part be due to different proportion of smokers in various studies [7,18]. Smoking is known to exert a detrimental effect on macrovascular disease and it increases the risk of early death and the microvascular complications of diabetes [25,26]. Thus, discontinuation of smoking is highly recommended in diabetic patients. Cessation of smoking is beneficial for the eye even though it does not affect diabetic retinopathy, since smoking increases cataract formation and the risk for age-related maculopathy [21] .

The strengths of our study are the excellent matching of the control group with the diabetic group for age, diabetes duration, sex distribution and proportion of type 1 and 2 diabetics. The numbers of type 1 and type 2 diabetic subjects were identical in both groups and this represents an excellent overview of the diabetic population. However, there are certain limitations to the current study. One of them is collection of the information by interview and questionnaire, which might be subject to recall bias. For example, self-reporting of alcohol consumption has been found to be influenced by social desirability bias [27]. Furthermore, alcohol consumption was recorded as the frequency of alcohol use instead of the quantitative amount of alcohol. However, there was only one diabetic patient who reported daily alcohol consumption and therefore, it is not likely that the amounts of alcohol consumed would have been only a few grams per day and therefore, they may be comparable to the previous study of Cundiff et al. [7]. Furthermore, differentiation between cause and effect is difficult in a cross-sectional study and it is problematic to eliminate confounding of unmeasured parameters. Although the data of presence of systemic hypertension exists, the lack of information about blood pressure in the diabetic control group influences the interpretation of results in physical activity, since the effect of exercise might be, in part, mediated through its effect on blood pressure.

Lifestyle intervention has been shown to be beneficial in preventing type 2 diabetes [28]. It is clear that we need to reduce the incidence of diabetes if we wish to combat its complications [29], but there is a need for multifactorial models to identify the best ways of to prevent diabetes complications. Recently a lifestyle intervention with diet and exercise did benefit patients with impaired glucose tolerance in terms of the development of diabetic retinopathy, but another intervention did not influence the development of nephropathy or neuropathy in Chinese population [30]. In diabetic retinopathy, diabetes duration and control are the main predictors of the disease and an intervention focussed on modifiable risk factors may not exceed their effect. However, cessation of smoking could be considered as the best intervention in preventing diabetes complications, not only in terms of diabetic retinopathy, but also for other complications.

In conclusion, the current case-control study found that alcohol consumption contributes to advanced forms of diabetic retinopathy. Patients with diabetic retinopathy are physically less active than diabetic control group and this phenomenon correlates with prevalence of neuropathy. However, diabetes control as well as low blood pressure and harmful plasma lipids remain crucial in preventing diabetic retinopathy in conjunction with screening to identify at-risk individuals.

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