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Impact of smoking and nicotine addiction on HbA_{1c} levels and diabetic microvascular complications

ABSTRACT

Introduction. In this study we aimed to determine whether a difference in complications between smokers and non-smokers exists in type 2 diabetes mellitus (T2DM) and to evaluate if there is a correlation between microvascular complications and Fagerström test score.

Material and methods. Patients with T2DM who attended the family medicine outpatient clinics were enrolled in the study. Smokers and non-smokers were compared according to their metabolic outcomes and presence of microvasculer complications. The level of smoking addiction was determined by Fagerström Test for Nicotine Dependence.

Results. Fasting blood glucose (FBG), low-density lipoprotein, systolic and diastolic blood pressures were found to be higher in smokers. The presence of neuropathy was significantly higher in smokers. The presence of retinopathy rate increased with increasing level of smoking addiction. The nicotine dependence test score were found to be positively correlated with HbA_{1c} and FBG levels whereas, negatively correlated with body mass index among smokers.

Conclusions. Assessing the cigarette smoking status of diabetic patients at the initial clinic visit and indicating the importance of smoking cessation should be the essential part of diabetes follow up program. (Clin Diabetol 2020; 9; 2: 112–117)

Key words: smoking, diabetes mellitus, microvascular complications, fagerstrom, HbA_{1c}

Introduction

Type 2 diabetes mellitus (T2DM) is a major health and socioeconomic problem for the community. According to the World Health Organisation's (WHO) data 422 million adults were living with DM in 2014 [1]. The number of adults with DM reached 451 million in 2017 and keeps increasing [2]. It is predicted that 642 million people will have DM and 481 million people will have impaired glucose tolerance by the year 2040 [3]. DM directly caused 1.6 million deaths in 2016 [4].

More than 1.1 billion people worldwide aged 15 years or older smoked tobacco in 2016 [4]. Smoking is the utmost known modifiable risk factor for many chronic diseases such as cardiovascular disease, chronic obstructive lung disease, and T2DM. Association between smoking and T2DM was investigated in previous studies [5]. According to a recent study, genetic polymorphisms in the nicotinic acetylcholine receptor genes may contribute to the association between smoking and T2DM [6]. Smoking is an independent risk factor for T2DM and both active smoking and exposure to passive smoke increase the risk of T2DM [7]. Compared with non-smokers with no exposure to passive smoke, there is an increased risk of T2DM among nonsmoker exposure with passive smoke [8]. Furthermore, smoking is found to be a risk factor for chronic complications of T2DM such as progression of diabetic nephropathy, peripheral polyneuropathy and diabetic retinopathy [9–13].

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This study aims to determine whether a difference in microvascular complications between diabetic patients who are smokers and non-smokers exists and to evaluate if there is a correlation between microvascular complications and smoking addiction.

Methods

Study population

T2DM patients who attended the family medicine outpatient clinics of a referral hospital were enrolled consecutively in the study. Patients with gestational diabetes, secondary diabetes; retinopathy, nephropathy or neuropathy not caused by diabetes; oncologic, inflammatory, immunologic or neuropsychiatric disease, ex-smokers and patients younger than 18 were excluded. A questionnaire regarding medical history and lifestyle factors was used during the clinic examinations.

Data collection and measurements

A structured checklist was used to record patients' demographics and laboratory data. We measured height to the nearest centimeter, weight to the nearest 0.5 kg, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) to the nearest mm Hg. Blood pressure was measured with a standard mercury sphygmomanometer while the patient was sitting after resting for 10 minutes and a mean of 3 readings was recorded. The subjects had their body weight (kg) assessed in the morning after overnight fasting. Bodyweight was measured using digital scales with the subjects only wearing underwear. BMI was calculated as weight (kg) divided by height (m) squared.

Smokers' severity of dependence was determined with The Fagerström Nicotine Dependence Test. In accordance with test scores, subjects were considered as minimally dependent (4 points or less), moderately dependent (5 to 7 points) and highly dependent (8 to 10 points).

Patients were examined by an ophthalmologist with an ophthalmoscope to determine retinopathy. Microaneurysm, retinal hard exudates, retinal edema, and retinal new vessels are evaluated positively for retinopathy. Blood creatinine levels, glomerular filtration rate (GFR) and elevated albuminuria of > 300 mg/24 h with concurrent presence of diabetic retinopathy and absence of signs of other forms of renal disease were used to evaluate nephropathy [14]. GFR is calculated with the CKD-EPI equation: $GFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (for women) (SCr is serum creatinine [mg/dL], κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1). Patients with GFR < 60 ml/min, > 300 mg albumin levels in 24-hour urine sample were diagnosed with nephropathy.

Patients were assessed for neuropathy using their medical history and examination. Symptoms especially worsened or occurring mostly during the night such as pain, dysesthesias (unpleasant sensations of burning and tingling), numbness and loss of protective sensation were considered as neuropathy symptoms. Comprehensive physical examination was performed to examine neuropathy include muscle power and tone examination, vibration perception examination with 120–200 Hz diapason, temperature and pinprick sensation examination, proprioception examination, 10-g monofilament to assess light-touch perception and ankle reflexes examinations are done to detect neuropathy [15]. Any abnormal examination result was evaluated as neuropathy. Electroneurography was not performed.

Patients' exercise and diabetes educational status were assessed. Patients who exercised at least 30 minutes per day and 3 to 7 days of the week were assessed as performing exercise regularly. Patients who had already been informed by a health professional including general practitioner or family physician about the course of T2DM, its complications and treatment options were considered educated. ADVIA 2400 Chemistry Systems/SIEMENS device was used to detect fasting plasma glucose (FBG), postprandial plasma glucose (PBG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), protein levels in 24-hour urine samples. HbA_{1c} levels are detected by (HPLC) Hb9210/PREMIER device which used boronate affinity technology.

Statistical analyses

We used IBM SPSS version 22 statistics for statistical analysis. Data's compatibility with normal distribution was determined by the Kolmogorov-Smirnov test. Comparisons between groups were made using Student's t test (for continuous variables) and the Chi-square test (for categorical variables). All values are expressed as the mean ± SD or number (%). We assumed $p < 0.05$ indicated significant differences.

Results

A total of 210 patients with T2DM (64.3% men) were enrolled into the study. The mean age of the patients was 49.7 ± 14.5, mean BMI was 26.2 ± 4.4 kg/m^2 and the mean T2DM duration was 8.3 ± 5.9 years. A total of 70 (33.3%) participants were active

Table 1. Comparison of demographical and clinical features of smokers and non-smokers

	Non-smoker	Smoker	p
Gender			
Women, n (%)	90 (64.3%)	45 (64.3%)	1.000
Men, n (%)	50 (35.7%)	25 (35.7%)	
Age (year) (MSD)	49.8 ± 14.7	49.4 ± 14.1	0.848
BMI [kg/m^2] (MSD)	26.1 ± 3.7	26.5 ± 5.4	0.507
Diabetes duration (year) (MSD)	8.1 ± 5.90	8.5 ± 6	0.679
Exercise			
No, n (%)	133 (95%)	61 (87.1%)	**0.043**
Yes, n (%)	7 (5%)	9 (12.9%)	
Education			
< High school, n (%)	63 (45%)	36 (51.4%)	**0.038**
≥ High school, n (%)	77 (55%)	34 (48.6%)	
Diabetes education			
No, n (%)	49 (35%)	16 (22.9%)	0.073
Yes, n (%)	91 (65%)	54 (77.1%)	
Systolic blood pressure (MSD)	120.3 ± 12.9	124.5 ± 15.3	**0.050**
Diastolic blood pressure (MSD)	73.5 ± 10	79.5 ± 10.2	**0.001**
Fasting blood glucose [mg/dL] (MSD)	163.1 ± 59.1	193.5 ± 84.8	**0.008**
Postprandial blood glucose [mg/dL] (MSD)	252.8 ± 96.5	281.2 ± 114.3	0.061
HbA_{1c} (%) (MSD)	8.8 ± 2	9.3 ± 2.3	0.133
Total cholesterol [mg/dL] (MSD)	179.9 ± 46.3	188.3 ± 46.7	0.216
LDL [mg/dL] (MSD)	102.2 ± 36.2	112.7 ± 33.4	**0.042**
HDL [mg/dL] (MSD)	41 ± 11.5	42.6 ± 13	0.382
TG [mg/dL] (MSD)	184.7 ± 134.4	171 ± 93	0.443

MSD — mean standard deviation; BMI — body mass ındex; HbA_{1c} — glycated hemoglobin; LDL — low-density lipoprotein; TG — triglyceride; HDL — high--density lipoprotein

smokers. Their mean smoking duration was 26.5 ± 17.5 pack-year. Comparison of demographical and clinical features of smokers and non- smokers are presented in Table 1. SBP (p = 0.05) and DBP (p = 0.001), FBG (p = 0.008) and LDL (p = 0.042) were found to be higher in smokers, respectively. Although the mean HbA_{1c} was found to be higher in smokers, it was not statistically significant. There were no significant differences between smokers and non-smokers in terms of their antidiabetic medications (Table 2).

The presence of neuropathy was significantly higher in smokers (Table 3). The presence of retinopathy rates increased with an increasing level of smoking addiction (p = 0.015) (Table 4). The nicotine dependence test score was found to be positively correlated with HbA_{1c} and FBG levels whereas, it negatively correlated with body mass index among smokers (p = 0,042) (Table 5).

Table 2. Antidiabetic drug usages among smoker and non-smoker patients

	Non-smokers n (%)	Smokers n (%)	p
Anti-diabetic medications			
Oral antidiabetic drugs	52 (37.1)	27 (38.6)	0.920
Insulin	36 (25.7)	19 (27.1)	
Insulin and oral antidiabetic drugs	52 (37.1)	24 (34.3)	

Discussion

Association between smoking and impaired glucose control was examined in many previous reports [16–18]. FBG levels were found to be higher in smokers compared to non-smokers in the present study.

Table 3. Comparison of microvascular complications of smokers and non-smokers

	Non-smokers n (%)	Smokers n (%)	p
Retinopathy			
Negative	99 (70.7)	48 (68.6)	0.749
Positive	41 (29.3)	22 (31.4)	
Nephropathy			
Negative	86 (61.4)	36 (51.4)	0.166
Positive	54 (38.6)	34 (48.6)	
Neuropathy			
Negative	113 (80.7)	43 (61.4)	**0.003**
Positive	27 (19.3)	27 (38.6)	

Table 4. Comparison of microvascular complications between smoking addiction levels

	Nicotine dependence			p
	Low n (%)	Medium n (%)	High n (%)	
Retinopathy				
Negative	21 (91.3)	14 (60.9)	13 (54.2)	**0.015**
Positive	2 (8.7)	9 (39.1)	11 (45.8)	
Nephropathy				
Negative	15 (65.2)	10 (43.5)	11 (45.8)	0.268
Positive	8 (34.8)	13 (56.5)	13 (54.2)	
Neuropathy				
Negative	17 (73.9)	15 (65.2)	11 (45.8)	0.128
Positive	6 (26.1)	8 (34.8)	13 (54.2)	

Table 5. Correlation of Fagerstrom Nicotine Depence Test score with clinical and laboratory features

	r	p
Age	0.082	0.5
BMI	–0.244	0.042
Fasting blood glucose	0.247	0.039
Post prandial blood glucose	0.211	0.080
HbA_{1c}	0.244	0.042
Total cholesterol	–0.40	0.741
LDL	0.078	0.520
TG	0.043	0.724
HDL	–0.183	0.128

BMI — body mass ındex; HbA_{1c} — glycated hemoglobin; LDL — low-density lipoprotein; Tg — triglyceride; HDL — high-density lipoprotein

In addition, PBG levels were higher in smokers whereas no statistically significant difference was found. Furthermore, HbA_{1c} levels were higher in smokers. This finding is inconsistent with other previous reports [16, 19]. All those increases could be partly explained by impaired glucose metabolism and insulin secretion due to smoking [20, 21].

It has been shown that achieving and maintaining glucose control is more difficult in smokers [16], hence microvascular complications can be more significant among diabetics who smoke. Smoking is one of the most important modifiable risk factors for the progression of microvascular complications and blood glucose dysregulation in diabetic patients. Smoking increases T2DM incidence and worsens T2DM complications. Although the mean HbA_{1c} was significantly higher in current smokers, the difference between smokers and never-smokers in FBG and PBG was controversial in previous studies [16].

In our study, the prevalence of cigarette smoking among diabetic patients was found to be 33.3%. This ratio is comparable with smoking ratio among the Turks. According to WHO, one-third of Turkish adults smoke cigarettes [22].

Smoking immediately increases SBP and DBP due to an increased in sympathetic nervous system activities and released of epinephrine, norepinephrine and vasopressin hormones [23, 24]. However, smoking's long term effect on blood pressure is not revealed [25]. Previous studies with older smokers found a larger difference in SBP compared to studies with younger smokers among T2DM patients [18]. It is an important outcome, considering that most of the smokers with T2DM were likely to be older. In this study, we found statistically significant differences in both DBP and SBP between smokers and non-smokers.

Previous studies indicated that smoking exerts a negative effect on lipid profiles [18, 26]. We found that LDL was significantly higher in smokers compared with non-smokers, as in previous reports [18]. Whereas, in HDL and TG statistically significant difference was not determined between smokers and non-smokers in our study.

One-third of T2DM patients have been diagnosed with microvascular complications at the time of diabetes diagnosis. However, the association between smoking and the development of microvascular complications has not been fully elucidated [27].

Retinopathy takes years to develop but eventually appears in nearly all diabetic patients. Pathogenesis of diabetic retinopathy related smoking has not been clearly established, impaired retinal microcirculation may be implicated [28]. Previous studies of the association between smoking and diabetic retinopathy had different results [28–30]. In our study, the presence of retinopathy rate was positively associated with the

Fagerström Test for Nicotine Dependence score. In addition, smokers have a higher rate of retinopathy than non-smokers, however, a statistically significant difference was not found.

A previous meta-analysis indicated that smoking is associated with the prevalence and incidence of diabetic neuropathy [12]. This study revealed that neuropathy has a significant difference between smokers and non-smokers, as in previous reports. Previous studies assessed that smoking is associated with diabetic nephropathy [9, 31]. Moreover, the smoking amount showed a dose-response relationship with albuminuria [31–33]. We also found that smokers have a higher rate of nephropathy comparing to non-smokers. However, the result was not statistically significant.

We acknowledge that our study has several limitations. First of all, although our study was conducted in one of the largest hospitals in Ankara which admits average of 6000 patients per day, it is a mono-centered study and the number of subjects in this study was not large. Therefore the generalisability to other population groups is uncertain. Second, we enrolled only T2DM patients. Consequently, we did not have chance to evaluate our findings in different diabetic groups. Third, this is a cross-sectional analysis, precluding inference of causality to the observed associations. The present findings should be replicated in a future study with a higher number of subjects, conducting a prospective assessment of each parameter.

Conclusions

In conclusion; our results indicate that smokers with T2DM are more likely to have diabetic neuropathy complication compared to non-smokers. In addition, the presence of retinopathy rate increased with increasing level of smoking addiction. Furthermore, the nicotine dependence test score were found to be positively correlated with HbA_{1c} and FBG levels whereas, negatively correlated with body mass index among smokers. Those findings reaffirm the need for clinical research to test tailored smoking cessation interventions for people with T2DM.

Smoking cessation might cause a reduction in microvascular complications. Unfortunately, there are limited data available to inform smoking cessation in people with diabetes. Therefore, it is thus of paramount importance to design intensive and innovative interventions to quit smoking in T2DM. The potential benefits of giving up smoking in those patients should be tested and evaluated in future studies.

All diabetes care professionals should be aware of the addictive and harmful effects of smoking.

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