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ORIGINAL RESEARCH

Association between Smoking and the Switching to Insulin Therapy in Type 2 Diabetes Patients

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Abstract

Background: Since no studies have been published on how active smoking affects switching to insulin therapy, we aimed to investigate the role of smoking on switching to insulin therapy in type 2 diabetes mellitus patients.

Methods: A total of 532 type 2 diabetes mellitus patients, who started insulin treatment due to the inability to achieve glycemic control with maximum oral anti-diabetic treatment, were included in the study. The patients were divided into three groups according to their smoking status at the beginning of insulin therapy: smokers (n = 114), ex-smokers (n = 178), and non-smokers (n = 240). Demographic and metabolic data, treatment regimens, and insulin start times were evaluated.

Results: The mean age of the patients was lowest in smokers and highest in non-smokers (p = 0.021). Non-smokers' duration of diabetes (p = 0.002) and years for switching to insulin treatment after diagnosis (p < 0.000) were statistically higher than smokers. Among smokers and ex-smokers, the time to start insulin therapy was earlier in smokers. HbA1c values of non-smokers were statistically similar to the other two groups. After controlling for age, duration of diabetes, and gender, smoking status was found to have an effect on the mean time to switching to insulin therapy.

Conclusions: Diabetes onset age and switching to insulin therapy is shorter in smokers than in non-smokers. These results reveal that glycemic control is impaired with smoking and patients have to switch to insulin treatment in a shorter time. Smoking cessation programs should also be offered to the diabetic population.

Keywords

Smoking, Type 2 diabetes mellitus, Diabetic complications, Insulin treatment, HbA1c

Introduction

Diabetes mellitus (DM) is characterized by impaired metabolism of carbohydrates, proteins, and lipids as a result of chronic hyperglycemia that results from complete or partial insufficiency of insulin secretion and/or insulin activity [1]. There are two main subtypes: insulin-dependent diabetes mellitus (type 1 diabetes mellitus, T1DM) and non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus, T2DM). T2DM is the most common form of DM and accounts for 90% to 95% of all diabetic patients [2]. Moreover, by 2030, the number of T2DM patients is expected to increase to 439 million [3]. The risk of developing T2DM is strongly linked to lifestyle, nutrition, and environmental factors. Therefore, it remains the most effective strategy to identify, and target known risk factors and to reduce disease prevalence and mortality [4]. In particular, smoking is one of the lifestyle factors that affects blood glucose in DM.

Smoking has been described as the second leading risk factor for early death and disability worldwide [5]. However, smoking has been suggested to be an independent and changeable risk factor for T2DM in both women and men [6-8]. The results of a recent meta-analysis of 88 observational prospective studies with approximately 6 million participants and 300 thousand T2DM cases showed that smokers have a 37% higher risk of developing T2DM than non-smokers [6]. As a result of this meta-analysis, a dose-response relationship was detected between smoking and T2DM development [6,9].

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Smoking is not only a risk factor for the development of T2DM but also has an effect on glycemic control. Various mechanisms have been proposed for the effect of smoking on glycemic control. Studies have revealed that smoking leads to systemic inflammation, increases oxidative stress, and endothelial dysfunction [10,11]. Additionally, smoking can cause changes in fat distribution and has a direct toxic effect on pancreatic β-cells through mechanisms of chronic inflammation and insulin resistance [12,13]. Furthermore, nicotine in cigarettes increases growth hormone and cortisol levels [14] and affects levels of peptides that control body weight and food intake [15], all of which can contribute to poor glycemic control.

The main goal of diabetes treatment is to achieve and maintain optimal blood glucose levels [16]. The first treatment in DM is lifestyle intervention and metformin. However, when the targeted glycemic factors are not achieved or maintained, rapid addition of drugs and new regimens should be adopted. If glycemic control cannot be achieved with oral antidiabetics (OADs), insulin treatment becomes inevitable [17]. Studies evaluating the relationship between smoking and glycemic control have been done lately. Although it has been reported that glycemic factors are impaired in smokers, there are no studies on how active smoking affects the switching to insulin treatment in diabetics. Moreover, patients with diabetes have limited awareness of the impact of smoking on diabetes outcomes [18]. They may also create several excuses to rationalize their never starting cessation attempts [19] as well for initiating insulin treatment when it is compulsory [20]. Therefore, we aimed to raise awareness about the impact of smoking on diabetes and its treatment, by investigating the role of smoking on the initiation of insulin therapy in patients with T2DM.

Materials and Methods

The institutional human study review committees of the Haseki Training and Research Hospital-Istanbul (28/2009; date: 28.05.2009) approved this case-control study. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all subjects. The data were collected retrospectively among the type 2 diabetic patients who were being followed up in the diabetes outpatient clinic and were under insulin treatment. A total of 532 T2DM patients aged 43 to 87 years whose glycemic control could not be achieved with maximum OAD treatment and initiation of insulin treatment, were included in the study. Exclusion criteria included T1DM, Latent Autoimmune Diabetes of Adults (LADA), acute complication of diabetes, non-diabetic kidney disease (secondary hyperparathyroidism, metabolic bone diseases, and electrolyte disorders), diabetic nephropathy (Glomerular Filtration Rate (GFR) ≤ 60 ml/min), chronic liver disease (chronic viral or nonviral hepatitis, patients with chronic alcohol use, metabolic diseases affecting the liver), liver enzyme levels (Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and prothrombin time) above the reference values, alcohol abuse, and those with acute or chronic pancreatitis.

The patients were divided into three groups according to their smoking status: current smokers (n = 114), ex-smokers (n = 178), and non-smokers (n = 240). Demographic and metabolic data, treatment regimens, and insulin therapy starting time were recorded. "Insulin Therapy Starting Time" is the mean time (years) recorded for switching to insulin treatment. Patients were also evaluated in three different groups according to the insulin treatment given: (i) Those who received OAD plus basal insulin; (ii) Who received pre-mixed insulin twice; and (iii) Those who received intensive insulin therapy. Pre-mixed insulin therapy was initiated in patients who could not achieve glycemic control with OAD plus basal insulin, and intensive insulin therapy was initiated in patients who could not achieve glycemic control with premixed insulin. Blood HbA1c values were analyzed by high-performance liquid chromatography (HPLC) using the Tosoh G7 (Belgium) analyzer.

The data were evaluated in IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) statistical package program. Descriptive statistics number of units (n), percent (%), mean ± standard deviation ($\overline{x}$ ± ss), smallest value (min), largest value (max), median (M), 25th percentile (Q1), and it is given as 75th percentile (Q3) values. The normal distribution of data of numerical variables was evaluated by the Shapiro Wilk normality test and Q-Q graphs. The homogeneity of the group variances was evaluated by the Levene test. Comparisons of two groups of continuous measurements were performed using the independent sample t-test or Mann-Whitney U test according to the normality test result. More than two-group comparisons were evaluated by One-Way ANOVA or Kruskal-Wallis analysis according to the normality test result. According to the results of variance homogeneity test, if there was a difference as a result of One-Way Variance Analysis, Tukey, or Tamhane multiple comparison test. In case of difference between Kruskal Wallis analyses, Dunn-Bonferroni multiple comparison test was used. Relationships between continuous variables were evaluated by Spearman correlation analysis according to the normality test result. One-way ANOVA was performed to evaluate whether smoking status and mean time for switching to insulin treatment was affected by the duration of diabetes, gender, and the age of the person. The relationship between categorical variables was examined in r x c tables by the Pearson Chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results

The study included a total of 532 people, 291 (54.6%) males, and 241 (45.3%) females. Descriptive statistics of the participants are given in Table 1. The mean age of the patients was 59.24 ± 9.06 years and the mean Body Mass Index (BMI) was 30.14 ± 5.19 kg/m^2. According to Table 1, of the patients were 114 (21.40%) smokers, 178 (33.50%) ex-smokers, 240 (45.10/%) non-smokers and cigarette smoking ranged from 3 to 105 packs per year. Of the patients, 209 (39.30%) received OAD + insulin, 172 (32.30%) received pre-mixed insulin, and 151 (28.40%) received intensive insulin therapy.

When the comparison was made according to smoking status, there was no statistically significant difference between the duration of insulin use (p = 0.829), diabetes onset age (p = 0.955), HbA1c values (p = 0.064), the marital status of the patients (p = 0.185), and the treatment protocols they received (p = 0.232)

Table 1: Descriptive statistics of continuous variables and frequency distribution of categorical variables.

Variable	***n***	$\bar{x}$ ***± sd (Min-Max)***
Age	532	59.24 ± 9.06 (43-87)
Diabetes Onset Age	532	48.65 ± 9.21 (32-81)
HbA1c	532	8.41 ± 1.93 (5.10-17.50)
Duration of Diabetes (Years)	532	10.58 ± 6.94 (1-40)
Insulin Switching Time (Years)	532	7.17 ± 5.96 (1-35)
Cigarette-Packet (Years)	292	35.69 ± 24.56 (3-105)
Smoking Cessation Period (Years)	177	9.98 ± 8.94 (1-40)
Body Mass Index (kg/m^2)	532	30.14 ± 5.19 (17.40-47.70)
Diabetes onset age in the smokers' group	114	48.25 ± 7.81 (32-66)
	n	**%**
Treatment protocol		
OAD + Insulin	209	39.30
Pre-mixed Insulin	172	32.30
Intensive Insulin	151	28.40
Smoking status 1		
Smoker	114	21.40
Ex-smoker	178	33.50
Non-smoker	240	45.10
Smoking status 2		
Smoker + Ex-smoker	292	54.90
Non-smoker	240	45.10
Duration of time after quitting smoking (years)		
0-5	76	42.94
5-10	42	23.73
10 to 15	15	8.47
15 to 20	19	10.73
> 20	25	14.12
Education status		
No Information in File	55	10.30
Unschooled	124	23.30
Literate	76	14.30
Primary school	212	39.80
Middle School	25	4.70
High school	23	4.30
University	17	3.20
Marital Status		
Married	458	86.10
Single	6	1.10
Widow	68	12.80

Table 2: Comparison results by smoking status.

	Smoker (*n* = 114)	Ex-Smoker (*n* = 178)	Non-Smoker (*n* = 240)	*p-value*
Age				
$\bar{x}$ ± *sd*	57.34 ± 8.31	59.16 ± 9.02	60.20 ± 9.33	**0.021**‡
Median (Q_1-Q_3)	56.50 (50.00-63.00)	58.00 (52.00-64.00)	59.00 (53.00-67.00)	
Duration of Diabetes (Year)				
$\bar{x}$ ± *sd*	9.10 ± 6.10	10.00 ± 6.82	11.73 ± 7.24	**0.002**⁺
Median (Q_1-Q_3)	8.00 (4.00-13.00)	9.00 (5.00-15.00)	10.00 (6.00-16.00)	
Time to Switch to Insulin After Diagnosis (Year)				
$\bar{x}$ ± *sd*	5.50 ± 5.01	6.72 ± 5.2	8.30 ± 6.32	**0.000**⁺
Median (Q_1-Q_3)	4.00 (2.00-8.00)	5.00 (2.00-10.00)	7.00 (3.00-11.50)	
Insulin Using Time				
$\bar{x}$ ± *sd*	3.82 ± 3.36	3.51 ± 3.32	3.64 ± 3.34	0.829⁺
Median (Q_1-Q_3)	3.00 (1.00-5.00)	3.00 (1.00-4.00)	2.00 (1.00-5.00)	
Diabetes Onset Age				
$\bar{x}$ ± *sd*	48.25 ± 7.81	49.16 ± 10.53	48.47 ± 8.78	0.955⁺
Median (Q_1-Q_3)	48.00 (43.00-54.00)	47.00 (42.00-56.00)	47.00 (42.00-53.00)	
HbA1c				
$\bar{x}$ ± *sd*	8.71 ± 2.14	8.12 ± 1.66	8.48 ± 1.99	0.064⁺
Median (Q_1-Q_3)	8.15 (7.20-10.00)	7.75 (6.80-9.30)	7.95 (7.10-9.45)	
BMI (*kg*/*m*²)				
$\bar{x}$ ± *sd*	28.97 ± 5.19	29.92 ± 4.66	30.86 ± 5.46	**0.009**⁺
Median (Q_1-Q_3)	28.55 (24.80-32.60)	29.20 (27.00-32.30)	30.40 (26.80-33.90)	
Educational Status (n, %)				**< 0.000**˙
No Information in File	22 (19.30)	28 (15.70)	5 (2.10)	
Unschooled	30 (26.30)	36 (20.20)	58 (24.20)	
Literate	22 (19.30)	27 (18.70)	27 (11.30)	
Primary school	33 (28.90)	57 (32.00)	122 (50.80)	
Middle School	3 (2.60)	11 (6.20)	11 (4.60)	
High school	3 (2.60)	11 (6.20)	9 (3.80)	
University	1 (0.90)	8 (4.50)	8 (3.30)	
Marital status (n, %)				0.185˙
The married	99 (86.80)	158 (88.80)	201 (83.80)	
Single	1 (0.90)	1 (0.60)	4 (1.70)	
Widow	14 (12.30)	19 (10.70)	35 (14.60)	
Treatment Protocol (n, %)				0.232˙
OAD + insulin	45 (39.50)	70 (39.30)	94 (39.20)	
Pre-mix insulin	31 (27.20)	57 (32.00)	84 (35.00)	
Intensive insulin	38 (33.30)	51 (28.70)	62 (25.80)	

‡One Way Variance Analysis (ANOVA); ⁺Kruskal Wallis Test; ˙Pearson Chi-Square Test

(Table 2). The mean age of the smokers was lower in the non-smokers compared to ex-smokers (p = 0.021). Non-smokers' duration of diabetes (p = 0.002) and years for switching to insulin treatment after diagnosis (p < 0.000) were statistically higher than smokers. Among smokers and ex-smokers, the time to start insulin therapy was earlier in smokers. Duration of insulin use and diabetes onset age were statistically similar between all groups but not statistically significant (p > 0.05), yet the duration of insulin use seemed to be longer in smokers. HbA1c

Table 3: Comparison results by insulin treatment protocol types.

	OAD + Insulin (n = 209)	Pre-Mix Insulin (n = 172)	Intensive Insulin (n = 151)	*p-value*
Age				
$\overline{x}$ ± *sd*	59.66 ± 9.03	59.49 ± 9.18	58.36 ± 8.99	0.366‡
Median (Q_1-Q_3)	58 (53-65)	59 (53-65.50)	58 (51-65)	
Duration of Diabetes (Year)				
$\overline{x}$ ± *sd*	12.10 ± 6.84	10.70 ± 7.76	8.36 ± 6.72	**< 0.000**⁺
Median (Q_1-Q_3)	11 (7-15)	10 (6-15)	6 (3-12)	
Time to Switch to Insulin After Diagnosis (Year)				
$\overline{x}$ ± *sd*	8.60 ± 6.04	7.51 ± 5.80	4.82 ± 5.29	**< 0.000**⁺
Median (Q_1-Q_3)	8 (4-11)	6 (3-10.5)	3 (1-6)	
Insulin Using Time (Year)				
$\overline{x}$ ± *sd*	3.67 ± 3.41	3.40 ± 3.02	3.86 ± 3.57	0.539⁺
Median (Q_1-Q_3)	3 (1-5)	2 (1-4)	3 (1-5)	
Diabetes Onset Age				
$\overline{x}$ ± *sd*	47.56 ± 8.85	48.80 ± 9.52	50.00 ± 9.20	**0.016**⁺
Median (Q_1-Q_3)	46 (41-52)	49 (42-56)	49 (43-55)	
HbA1c				
$\overline{x}$ ± *sd*	8.38 ± 1.74	8.49 ± 2.19	8.37 ± 1.88	0.929⁺
Median (Q_1-Q_3)	8 (7-9.5)	7.95 (6.9-9.4)	8 (7-9.2)	
BMI (*kg*/*m*²)				
$\overline{x}$ ± *sd*	30.79 ± 5.31	29.50 ± 5.54	29.98.02 ± 4.50	**0.045**⁺
Median (Q_1-Q_3)	30.4(27.1-33.7)	28.75(25.55-33.3)	29.80(26.8-32.7)	
Cigarette Pack/Year	**(*n* = 115)**	**(*n* = 88)**	**(*n* = 89)**	
$\overline{x}$ ± *sd*	33.09 ± 23.72	36.18 ± 23.56	38.56 ± 26.46	0.341⁺
Median (Q_1-Q_3)	30(15-45)	34.50(15.5-50)	30(20-60)	

‡One Way Variance Analysis (ANOVA); ⁺Kruskal Wallis Test

values of smokers were statistically higher than those of ex-smokers but not statistically significant (p = 0.064). BMI values were similar between those of ex-smokers and non-smokers, yet they were higher than those of smokers (p = 0.009). Educational status distribution was statistically different from smoking groups (p < 0.000). The number of primary school graduates was higher in the non-smoker group.

Table 3 shows the correlation between insulin treatment protocols and other parameters. Age, duration of insulin use, HbA1c values, the number of cigarettes consumed, and marital status were statistically similar, depending on the type of treatment protocol. Diabetes onset age was statistically lower in OAD+ insulin group (p = 0.016). The diabetes duration of the intensive insulin group was statistically lower than the other two groups (p < 0.000). The time to start insulin therapy was statistically different in all three groups (p < 0.001), and patients who received intensive insulin therapy began to receive insulin therapy much earlier. At OAD + insulin group, BMI values were statistically higher than the premixed insulin group (p = 0.045). The number of cigarettes consumed was similar between all groups.

When we evaluated the smokers and ex-smokers as a single group and compared with non-smokers, non-smokers were statistically older than smoker/ex-smoker group (p = 0.027). The duration of diabetes was less in smokers/ex-smokers (p = 0.001), yet, switching to insulin treatment after diagnosis was sooner (p < 0.001) than non-smokers, revealing the possible negative impact of a single previous cigarette (Table 4). The duration of diabetes (p = 0.005) and the time for switching to insulin treatment after diagnosis (p < 0.002) were longer in women than in men (Table 5). Smoking cessation time was not significantly associated with HbA1c (rho = 0.001; p = 0.998) and insulin initiation time (rho = 0.028; p = 0.712) (Table 6).

Table 4: Comparison results by smoking status.

	Smokers and Ex-smokers	Non-Smokers	*p-value*
Age	**(*n* = 292)**	**(*n* = 240)**	
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	58.45 ± 8.78 58 (52-63)	60.20 ± 9.33 59 (53-67)	**0.027**†
Duration of Diabetes (Year)			
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	9.65 ± 6.55 8 (5-14)	11.72 ± 7.24 10 (6-16)	**0.001**⁺
Time to Switch to Insulin After Diagnosis (Year)			
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	6.25 ± 5.48 5 (2-9)	8.30 ± 6.32 7 (3-11.5)	**0.000**⁺
Insulin Use Time (Year)			
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	3.63 ± 3.33 3 (1-4.5)	3.64 ± 3.34 2 (1-5)	0.973⁺
Diabetes Onset Age			
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	48.84 ± 9.56 48 (42-55)	48.47 ± 8.78 47 (42-53)	< 0.761⁺
HbA1c			
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	8.35 ± 1.88 8 (6.9-9.4)	8.48 ± 1.99 7.95 (7.1-9.45)	0.495⁺
BMI (*kg*/*m*²)			
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	29.55 ± 4.89 29 (26.25-32.4)	30.86 ± 5.46 30.40 (26.8-33.9)	0.07⁺
Treatment Protocol (n, %)			0.374*
OAD + insulin	115 (0.39)	94 (0.39)	
Pre-mix insulin	88 (0.3)	84 (0.35)	
Intensive insulin	89 (0.31)	62 (0.26)	

†Independent Sample *t-Test;* ⁺Mann Whitney *U* Test; *Pearson Chi-Square Test

Table 5: Comparison results by gender.

	Male **(*n* = 291)**	Female **(*n* = 241)**	***p-value***
Duration of Diabetes (Year)			
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	9.8 ± 6.57 8.0 (5.0-13.0)	11.53 ± 7.2 10.0 (6.0-15.0)	**0.005**⁺
Time to Switch to Insulin After Diagnosis (Year)			
$\bar{x}$ ± *sd* *Median* (Q_1-Q_3)	6.5 ± 5.63 5.0 (2.0-10.0)	7.99 ± 6.24 6.0 (3.0-11.0)	**0.002**⁺

⁺Mann Whitney *U* Test

Table 6: Examination of the relationship between smoking cessation time and HbA1c and insulin initiation time times.

	HbA1c %	Insulin Initiating Time (*Year*)
Smoking cessation time	**(n = 177)**	**(n = 177)**
rho (p-value)	0.001 (0.998)	0.028 (0.712)

rho: Spearman correlation coefficient

One-way analysis of covariance analysis was performed to evaluate whether smoking status had an effect on the mean time for switching to insulin therapy, controlling for age, duration of diabetes, and gender. There was a significant difference in the mean time to switch to insulin therapy after diagnosis [F(1,529) = 6.893, p = 0.001] between the smoking status, whilst adjusting for age. According to the post hoc test results, there is a significant difference between smokers and non-smokers (p = 0.020), ex-smokers and non-smokers (p = 0.040), while there is no significant difference between ex-smokers and smokers (p = 0.489). There was a significant difference in the mean time to switch to insulin therapy after diagnosis [F(2,528) = 6.452, p = 0.002] between the smoking status, whilst adjusting for gender. According to the post hoc test results, there is a significant difference between smokers and non-smokers (p = 0.001), while there is no significant difference between ex-smokers and non-smokers (p = 0.215), ex-smokers and smokers (p = 0.160). In the mean time, there was a significant difference for switching to insulin therapy after diagnosis [F(2,528) = 3.250, p = 0.040] between the smoking status, whilst adjusting for duration of diabetes. According to the post hoc test results, there is a significant difference between smokers and non-smokers (p = 0.011), while there isn't between ex-smokers and non-smokers (p = 0.295), ex-smokers and smokers (p = 0.117). These results showed us the negative effect of smoking a single cigarette on the diabetic patient, regardless of age, gender, and duration of diabetes (Table 7).

Discussion

Although the causal relationship between the cigarettes consumed and T2DM has been established, the molecular mechanisms are not fully understood. However, researchers have reported that some mechanisms contribute to the causality relationship. Nicotine, the biologically active molecule of cigarettes, has been found to impair the function and structure of islet β- cells [21,22]. Thus, glucose homeostasis, which plays an important role at the beginning of T2DM, is disrupted [23]. Bile acids, which are of great importance in the regulation of glucose metabolism, are suppressed by smoking [24]. Another effect of smoking on the gastrointestinal tract is that it causes changes in the composition of the intestinal microbiome, which plays a vital role in the pathophysiology of T2DM [23]. In addition, smoking affects the functions of the nervous system, such as the hypothalamus and vagus, which are involved in the regulation of glucose metabolism [25,26]. Systemic inflammation from smoking also partially contributes to this relationship [27]. Although these pathological pathways have been determined to explain the causality between smoking and T2DM, further research is needed on genetics, epigenetics, and omics for the prevention and treatment of T2DM [23].

Numerous epidemiological studies showing the relationship between smoking and T2DM have been conducted. In a meta-analysis of cohort studies, it was reported that active smokers had a 1.44-fold (95% CI 1.31, 1.58) higher risk of developing T2DM than nonsmokers [7]. Moreover, according to these studies, it was revealed that those who use 20 cigarettes and more per day have a relative risk of developing T2DM 1.61, while those who smoke less than 20 cigarettes have a relative risk of developing T2DM 1.29. These results show that there is a dose-response association between smoking and developing T2DM [7]. In our study, the mean age of diabetic patients who smoke was lower than that of non-smokers, yet the age of onset of diabetes was similar. Previous studies have shown that smoking is an independent risk factor for T2DM [6-9]. The finding that smokers, in this study, did not have an early onset T2DM is inconsistent with the results of these studies. Although studies have revealed a dose-response relationship between smoking and T2DM risk, we did not find any correlation between the number of

Table 7: The effect of smoking on initiating insulin therapy by controlling for duration of age, duration of diabetes and gender.

	F (p-value)	η_p^2	R^2	Adjusted R^2
Model I				
Constant	9.731 (0.002)	0.018	0.128	0.123
Smoking status	6.893 (0.001)	0.025		
Age	55.917 (0.000)	0.096		
Model II				
Constant	43.712 (0.000)	0.076	0.039	0.034
Smoking status	6.452 (0.002)	0.024		
Gender	2.170 (0.141)	0.004		
Model III				
Constant	9.468 (0.002)	0.018	0.754	0.752
Smoking status	3.250 (0.040)	0.012		
Duration of Diabetes(Year)	1540.151 (0.000)	0.745		

η_p^2: Impact magnitude (Partial eta square); *sd*: Degree of freedom; One-way Covariance Analysis (One-way ANCOVA).

cigarettes consumed and the age of onset of diabetes in our study.

With revealing the causal relationship between smoking and T2DM, studies have focused on the relationships between smoking and glycemic control. In a large cross-sectional study of 2704 men and 3385 women, followed by the European Cancer Investigation (EPIC-Norfolk) study, smoking was reported to cause higher HbA1c concentrations independently. Also, it has been shown that smoking increased at the level of HbA1c by 0.12% per 20 pack-years in both genders [28]. If smoking increases the level of HbA1c even in people without diabetes, knowing how smoking affects HbA1c in people with diabetes is important for the development and effective management of diabetes. However, the extent that smoking has impaired glycemic control in diabetic patients has not been fully studied, and the limited results of the studies are inconsistent. While some studies have reported that active smoking causes an increase in HbA1c levels [29,30], other studies did not report changes [31,32]. In addition, Ohkuma, et al. [33] showed that active smoking causes an increase in HbA1c levels, and this supports a positive dose-dependent relationship. Also, researchers have identified improvements in HbA1c levels over the years following smoking cessation. According to these results, these findings may strengthen the benefit of smoking cessation in diabetic patients. In our study, the HbA1c levels of smokers were higher than those who were ex-smoking; however, they were similar to those who did not smoke. Our results are in line with the study results stating that smoking does not change the HbA1c levels. Therefore, more study results are needed on this topic.

Gradual deterioration of glycemic control over time is characteristic in T2DM patients. Therefore, to prevent diabetic complications, effective maintenance of glycemic targets from the moment of diagnosis is the most effective way of treatment and is highly recommended [23,34-36]. However, achieving glycemic goals is not always easy for patients and healthcare providers. Oral antidiabetic drugs (OAD) are often insufficient to maintain glycemic control, and disease therapy may need to be gradually intensified, including insulin therapy [37]. In the UK Prospective Diabetes Study (UKPDS) study [38], it was reported that more than half of the patients diagnosed with T2DM needed insulin therapy in addition to OADs within 6 years because glycemic control was not achieved with OAD. In another study, it was reported that 25% of patients with T2DM were prescribed insulin within 6 years of starting OAD treatment, and this rate increased to 42% after 10 years [39]. In this study, the average time to switch to insulin for all patients was 7.17 years. However, the average time to switch to insulin therapy for smoking patients was 5.50 years, which was much shorter than ex-smokers and non-smokers. Studies reveal that diabetes risk remains in heavy and extreme smokers even after smoking cessation [40]. In our study, it took ex-smokers 6.72 years to switch to insulin therapy, which was statistically shorter than non-smokers (8.30 years). According to these results, it can be stated that smoking reduces the duration to switch to insulin treatment of type 2 diabetes patients**.** Smoking is known to indirectly stimulate the secretion of endothelin-1 (ET-1) [41]. It has been reported that ET-1 induces the production of proinflammatory cytokines and increases insulin resistance by affecting the activation of pancreatic islet cells; as a result, affecting the development of diabetes [42,43]. We think that one of the reasons for smokers to switch to insulin treatment in a shorter time is the indirect contribution of ET-1.

In conclusion, we showed that switching to insulin therapy is shorter in smokers than in non-smokers. Our findings suggest that glycemic control is impaired with smoking and patients have to switch to insulin treatment in a shorter time. Previous studies mainly focused on the impact of smoking on macro/microvascular complications in type 2 diabetic patients, but our study emphasizes the impact of smoking on treatment options. There is a need for more studies on the effect of smoking on glucose metabolism and insulin resistance. For this specific population, smoking and smoking cessation programs should be offered keeping in mind that risks remained even after smoking cessation.

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