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ORIGINAL ARTICLE

Does Smoking Speed up Switching To Insulin Therapy in Type 2 Diabetes Patients?

ZUHAL AYDAN SAGLAM[1], TAYYIBE SALER[2], ŞENNUR KÖSE[3]
[1]*Department of Family Medicine Istanbul Training and Research Hospital University of Health Sciences, Istanbul, 34098, TURKEY*
[2]*Department of Internal Medicine Adana City Hospital University of Health Sciences, Adana, 01370, TURKEY*
[3]*Istanbul Training and Research Hospital Org. Abdurrahman Nafiz Gürman Cad. Etyemez, Samatya Istanbul, 34098, TURKEY*
Corresponding author: Şennur Köse, Email: drsennurkose@gmail.com, Cell: +90 506 2977284

ABSTRACT

Objectives: 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 617 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=143), ex-smokers (n=189), and non-smokers (n=285). Demographic and metabolic data, treatment regimens, and insulin start times were evaluated.

Results: The age of onset of diabetes was lower in smokers than non-smokers. Non-smoker duration of diabetes ($p=0.001$) and switching to insulin treatment ($p<0.001$) were statistically higher than smokers. HbA1c values of non-smokers were statistically similar to the other two groups.

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. 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 [1]. Moreover, by 2030, the number of T2DM patients is expected to increase to 439 million [2]. 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 [3]. 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 [4]. However, smoking has been suggested to be an independent and changeable risk factor for T2DM in both women and men [5]. 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 [5]. As a result of this meta-analysis, a dose-response relationship was detected between smoking and T2DM development [5].

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 [6]. 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 [7]. Furthermore, nicotine in cigarettes increases growth hormone and cortisol levels [8] and affects levels of peptides that control body weight and food intake [9], all of which can contribute to poor glycemic control.

The main goal of diabetes treatment is to achieve and maintain optimal blood glucose levels [10]. 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 anti-diabetics (OADs), insulin treatment becomes inevitable [11]. 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. Therefore, we aimed to investigate the role of smoking on the initiation of insulin therapy in patients with T2DM in the study.

MATERIALS AND METHODS

Institutional human studies review committees 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. A total of 617 T2DM patients aged 20 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), an acute complication of diabetes, non-diabetic kidney disease (secondary hyperparathyroidism, metabolic bone diseases, and electrolyte disorders), diabetic nephropathy (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 (ALT, 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 at the start of insulin therapy: smokers (n=143), ex-smokers (n=189), and non-smokers (n=285). Demographic and metabolic data, treatment regimens, and insulin initiation time were recorded. 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 ($\bar{x}$ ± 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 time and insulin treatment start times affected body mass index, 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 617 people, 339 (54.90%) males, and 278 (45.10%) females. The mean age of the patients was 56.74 ± 11.11 and the mean BMI was 29.87 ± 4.94. According to findings, of the patients were 143 (23.20%) smokers, 189 (30.60%) ex-smokers, 285 (46.20%) non-smokers and cigarette smoking ranged from 3 to 105 packs per year. Of the patients, 230 (37.30%) received OAD + insulin, 208 (33.70%) received pre-mixed insulin, and 179 (29.00%) 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=0.995), the marital status of the patients (p=0.317), and the treatment protocols they received (p=0.794) (Table 1a). The mean age of the smokers and the age of onset of diabetes were lower than in the ex-smokers compared to non-smokers (p<0.001). Non-smokers' duration of diabetes (p = 0.001) and switching to insulin treatment (p<0.001) were statistically higher than smokers. The time to switch to insulin between smokers and ex-smoker was statistically similar. HbA1c values of smokers were statistically higher than those of ex-smokers (p=0.011). HbA1c values of non-smokers were statistically similar to the other two groups. BMI values were similar between those of ex-smokers and those of non-smokers, and the values of these two groups were higher than those who smoked (p=0.007). Educational status distribution was statistically different from smoking groups (p<0.001). The number of primary school graduates was higher in the non-smoking group.

Table 1a: Comparison results by smoking status

	Smoker	Ex-Smoker	Non-Smoker	p-value	Smokers + Ex-smokers	Non-Smokers	p-value
Age	(n=143)	(n=189)	(n=285)		(n=332)	(n=285)	
$\bar{x}$±sd Median (Q_1-Q_3)	54.03±10.77 54(47-61) [a]	58.23±9.73 58(51-63) [b]	57.10±11.91 57(50-66) [b]	0.002‡	56.42±10.39 56(50-63)	57.10±11.91 57(50-66)	0.456†
Duration of Diabetes (Year)	(n=143)	(n=189)	(n=285)		(n=332)	(n=285)	
$\bar{x}$±sd Median (Q_1-Q_3)	9.36±7.14 8(4-13) [a]	10.25±7.27 9(5-15) [ab]	11.75±7.55 10(6-16) [b]	0.001+	9.87±7.22 8(4-14)	11.75±7.55 10(6-16)	0.001+
Time to Switch to Insulin After Diagnosis (Year)	(n=143)	(n=188)	(n=285)		(n=331)	(n=285)	
$\bar{x}$±sd Median (Q_1-Q_3)	5.74±5.90 4(1-8) [a]	6.91±6.13 5(2-10) [a]	8.37±6.76 7(3-11.50) [b]	<0.001+	6.40±6.053 5(1-9)	8.37±6.76 7(3-11.50)	<0.001#
Insulin Using Time (Year)	(n=143)	(n=189)	(n=285)		(n=332)	(n=285)	
$\bar{x}$±sd Median (Q_1-Q_3)	3.87±4.13 3(1-5)	3.62±3.57 3(1-4.5)	3.61±3.38 3(1-4)	0.995	3.73±3.81 3(1-5)	3.61±3.37 3(1-4)	0.918#
Diabetes Onset Age	(n=98)	(n=0)	(n=129)		(n=98)	(n=129)	
$\bar{x}$±sd Median (Q_1-Q_3)	26.94±23.74 37(0-47.25) [a]	-	47.31±10.29 47(41-54) [b]	<0.001+	26.94±23.74 37(0-47.25)	47.31±10.29 47(41-54)	<0.001#
HbA1c	(n=139)	(n=184)	(n=279)		(n=323)	(n=279)	
$\bar{x}$±sd Median (Q_1-Q_3)	8.88±2.23 8.50(7.20-10.10) [a]	8.13±1.67 7.75(6.90-9.30) [b]	8.84±5.82 8(7.10-9.70) [a. b]	0.011+	8.45±1.96 8.10(7-9.50)	8.82±5.82 8(7.10-9.70)	0.676#
BMI (kg/m^2)	(n=143)	(n=189)	(n=285)		(n=332)	(n=285)	
$\bar{x}$±sd	28.55±4.81	30.13±4.50	30.37±5.17	0.007+	29.45±4.69	30.37±5.16	0.072#

Median (Q_1-Q_3)	28.80(25.05-32.08) [a]	29.83(27-32.67) [b]	29.73(27.02-33.18) [b]		29.35(26.23-32.24)	29.73(27.02-33.18)	
Educational Status (n, %)	(n=143)	(n=189)	(n=285)	<0.001*	(n=332)	(n=285)	<0.001+
No Information in File	33 (23.10) [a]	28 (14.80) [a]	5 (1.80) [b]		61 (18.40) [a]	5 (1.80) [b]	
Unschooled	36 (25.20) [a]	39 (20.60) [a]	62 (21.80) [a]		75 (22.60) [a]	62 (21.80) [a]	
Literate	24 (16.80) [a]	28 (14.80) [a]	32 (11.20) [a]		52 (15.70) [a]	32 (11.20) [a]	
Primary school	38 (26.60) [a]	61 (32.30) [a]	142 (49.80) [b]		99 (29.80) [a]	142 (49.80) [b]	
Middle School	5 (3.50) [a]	12 (6.30) [a]	18 (6.30) [a]		17 (5.10) [a]	18 (6.30) [a]	
High school	4 (2.80) [a]	12 (6.30) [a]	15 (5.30) [a]		16 (4.80) [a]	15 (5.30) [a]	
University	3 (2.10) [a]	9 (4.80) [a]	11 (3.90) [a]		12 (3.60) [a]	11 (3.90) [a]	
Marital status (n, %)	(n=143)	(n=189)	(n=285)	0.317*	(n=332)	(n=285)	0.281*
The married	123 (86)	169 (89.40)	239 (83.90)		292 (88)	239 (83.90)	
Single	4 (2.80)	1 (0.50)	8 (2.80)		5 (1.50)	8 (2.80)	
Widow	16 (11.20)	19 (10.10)	38 (13.30)		35 (10.50)	38 (13.30)	
Treatment Protocol (n, %)	(n=143)	(n=189)	(n=285)	0.794*	(n=332)	(n=285)	0.432*
OAD + insulin	54 (37.80)	71 (37.60)	105 (36.80)		125 (37.70)	105 (36.80)	
Pre-mix insulin	45 (31.50)	60 (31.70)	103 (36.10)		105 (31.60)	103 (36.10)	
Intensive insulin	44 (30.80)	58 (30.70)	77 (27)		102 (30.70)	77 (27)	

‡ One Way Variance Analysis (ANOVA)
+ Kruskal Wallis Test
* Pearson Chi-Square Test
† Independent Sample t-Test
# Mann Whitney U Test
The superscript a and b show the difference between measurements in the same group. The measurements with the same letter are similar.

When we evaluated the smokers and ex-smokers as a single group and compared with non-smokers, the duration of diabetes (p=0.001), the switching to insulin treatment after diagnosis (p<0.001), and the age of onset of diabetes (p<0.001) were higher in non-smokers. There was no difference between the groups in terms of other parameters (Table 1a).

Table 1b shows the comparison between insulin treatment protocols and other parameters. The duration of insulin use, diabetes onset age, HbA1c values, the number of cigarettes smoked, and marital status were statistically similar, depending on the type of treatment protocol. The ages of the patients who received OAD + insulin treatment were statistically higher than those who received intensive insulin treatment (p=0.019). The diabetes duration of the intensive insulin group was statistically lower than the other two groups (p<0.001). 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. OAD + insulin group BMI values are statistically higher than the premixed insulin group (p=0.039).

Table 1b: Comparison results by insulin treatment protocol types

	OAD + Insulin	Pre-Mix Insulin	Intensive Insulin	p-value
Age	(n=230)	(n=208)	(n=179)	0.019‡
$\bar{x}$±sd Median (Q_1-Q_3)	58.32 ± 9.90 57 (52-65) [a]	56.15 ± 12.20 57 (49-64) [a. b]	55.39 ± 11.07 56 (48-63) [b]	
Duration of Diabetes (Year)	(n=230)	(n=208)	(n=179)	<0.001+
$\bar{x}$±sd Median (Q_1-Q_3)	12.34 ± 7.34 11 (7-16) [a]	11.03 ± 7.53 10 (6-15) [a]	8.33 ± 6.83 6 (3-12) [b]	
Time to Switch to Insulin After Diagnosis (Year)	(n=229)	(n=208)	(n=179)	<0.001+
$\bar{x}$±sd Median (Q_1-Q_3)	8.97 ± 6.68 8 (4-12) [a]	7.69 ± 6.51 6 (2-10.75) [b]	4.76 ± 5.23 3 (1-6) [c]	
Insulin Using Time (Year)	(n=230)	(n=208)	(n=179)	0.572+
$\bar{x}$±sd Median (Q_1-Q_3)	3.54 ± 3.30 3 (1-5)	3.62 ± 3.84 3 (1-4)	3.91 ± 3.74 3 (1-5)	
Diabetes Onset Age	(n=88)	(n=68)	(n=71)	0.285+
$\bar{x}$±sd Median (Q_1-Q_3)	38.23 ± 20.02 44 (35.25-51)	41.41 ± 19.39 46 (36-53)	36.10 ± 20.79 42 (27-51)	
HbA1c	(n=226)	(n=199)	(n=177)	0.585+
$\bar{x}$±sd Median (Q_1-Q_3)	8.44 ± 1.73 8.1 (7.17-9.62)	8.48 ± 2.22 8 (6.90-9.40)	9.05 ± 7.15 8.10 (7.10-9.60)	
BMI (kg/m^2)	(n=230)	(n=208)	(n=179)	0.039+
$\bar{x}$±sd Median (Q_1-Q_3)	30.45 ± 5.04 30.06 (26.93-33.56) [a]	29.37 ± 5.23 28.95(25.88-32.18) [b]	29.73 ± 4.37 29.61(26.9-32.34) [a. b]	
Cigarette Pocket/Year	(n=125)	(n=105)	(n=102)	0.467+
$\bar{x}$±sd Median (Q_1-Q_3)	31.62 ± 23.35 25 (14-40)	33.77 ± 22.89 30 (15-45)	35.96 ± 25.92 25.50 (20-52.50)	
Educational Status (n, %)	(n=230)	(n=208)	(n=179)	<0.001*
No Information in File	17 (7.40) [a]	36 (17.30) [b]	13 (7.30) [a]	
Unschooled	78 (33.90) [a]	32 (15.40) [b]	27 (15.10) [b]	
Literate	29 (12.60) [a. b]	21 (10.10) [b]	34 (19) [a]	
Primary school	73 (31.70) [a]	92 (44.20) [b]	76 (42.50) [a. b]	

Middle School	11 (4.80) [a]	11 (5.30) [a]	13 (7.30) [a]	
High school	13 (5.70) [a]	8 (3.80) [a]	10 (5.60) [a]	
University	9 (3.90) [a]	8 (3.80) [a]	6 (3.40) [a]	
Marital status (n, %)	(n=230)	(n=208)	(n=179)	0.533*
The married	196 (85.20)	177 (85.10)	158 (88.30)	
Single	4 (1.70)	7 (3.40)	2 (1.10)	
Widow	30 (13)	24 (11.50)	19 (10.60)	

‡ One Way Variance Analysis (ANOVA)
+ Kruskal Wallis Test
* Pearson Chi-Square Test
The superscripts a, b, c indicate the difference between measurements in the same group. The measurements with the same letter are similar.

Spearman correlation analysis was performed to investigate the relationship between the variables. According to the results of the analysis, there was no statistically significant effect of BMI (kg/m2) on smoking time (rho=0.008; p=0.890) and time to start insulin therapy (rho=-0.076; p=0.059). However, the relationship between the duration of diabetes and the duration of starting insulin treatments was statistically significant (rho=0.850; p<0.001). In addition, when the duration of diabetes, time to starting insulin therapy, and smoking time were all analyzed according to age, there was a positive correlation for each rho=0.327; p<0.001, rho=0.292; p<0.001, and rho=0.260; p<0.001, respectively. However, no statistically significant correlation was found between the starting time to insulin therapy and smoking time (rho=-0.042; p=0.444) or diabetes time and smoking time (rho=0.067; p=0.224).

The duration of starting insulin therapy was similar in men and women, but the duration of diabetes (p=0.001) and the switching to insulin treatment after diagnosis (p<0.001) were higher in women than in men (Table 2).

Table 2: Comparison results by gender

	Male	Female	p-value
Duration of Diabetes (Year)	(n=339)	(n=278)	0.001*
$\bar{x}$±sd Median (Q_1-Q_3)	9.80±6.90 8 (8-13)	11.80±7.80 10 (6-16)	
Starting of Insulin Therapy (Year)	(n=339)	(n=278)	0.482
$\bar{x}$±sd Median (Q_1-Q_3)	3.50±3.50 3 (1-4)	3.70±3.60 3 (1-5)	
Time to Switch to Insulin After Diagnosis (Year)	(n=338)	(n=278)	<0.001*
$\bar{x}$±sd Median (Q_1-Q_3)	6.50±5.90 5 (1.00-9.30)	8.20±6.90 6.50 (3.00-11.50)	

* Mann Whitney U Test

One-way covariance analysis was carried out to evaluate whether smoking time, diabetes duration, BMI, gender, and age had an effect on the duration of insulin therapy. Four different models were created to examine each effect. According to Table 3, no statistically significant variable was found in the first and third models. According to Model II, when smoking duration and diabetes duration were evaluated together, it was observed that the duration of diabetes was effective on the duration of starting insulin treatment. According to Model IV, when smoking time and age were evaluated together, it was determined that age was effective on starting insulin treatment.

According to the result of spearman correlation analysis, no statistically significant association was found between smoking cessation time and the HbA1c variable (rho=0.001; p=0.990). No statistically significant association was found between smoking cessation time and insulin initiation times (rho=0.024; p=0.747).

Table 3: Investigation of the effects of starting insulin therapy, smoking time and body mass index (BMI), duration of diabetes, gender, and age.

	F (p-value)	η_p^2	R^2	Adjusted R^2
Model I				
Constant	0.120 (0.730)	0.000	0.245	0.025
Smoking period (years)	1.253 (0.167)	0.153		
BMI (kg / m2)	0.343 (0.558)	0.001		
Model II				
Constant	0.226 (0.635)	0.001	0.799	0.727
Smoking period (years)	0.574 (0.975)	0.076		
Duration Of Diabetes	46.327 (<0.001)	0.160		
Model III				
Constant	12.333 (0.001)	0.191	0.191	0.047
Smoking period (years)	1.070 (0.379)	0.046		
Gender	0.334 (0.564)	0.088		
Model IV				
Constant	1.055 (0.305)	0.004	0.309	0.062
Smoking period (years)	1.288 (0.139)	0.157		
Age	5.528 (0.020)	0.022		

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

CONCLUSIONS

Although the causal relationship between cigarette 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 [12]. Thus, glucose homeostasis, which plays an important role at the beginning of T2DM, is disrupted [13]. Bile acids, which are of great importance in the regulation of glucose metabolism, are suppressed by smoking [14]. 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 [12]. In addition, smoking affects the functions of the nervous system, such as the hypothalamus and vagus nerve, which are involved in the regulation of glucose metabolism [15]. Systemic inflammation from smoking also partially contributes to this relationship [16]. 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 [6].

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 [17]. Moreover, with 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 [17]. In our study, the mean age of diabetic patients who smoke was lower than that of non-smokers. In addition, the age of onset of diabetes was lower in smokers than non-smokers. Previous studies have shown that smoking is an independent risk factor for T2DM [5,17]. The finding that smokers, in this study, had early-onset T2DM is consistent 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 amount of cigarettes used 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 gender [18]. 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 [19], other studies did not report changes [20]. In addition, Ohkuma et al. [21] 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 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 [13]. 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. In the UKPDS study [22], 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 [23]. In this study, the average time to switch to insulin for all patients was 7.31 years. However, the average time to switch to insulin therapy for smoking patients was 5.74 years, which was much shorter than ex-smokers and non-smokers. Ex-smokers took 6.91 years to switch to insulin therapy, which was statistically shorter than non-smokers (8.37 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) [24]. 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 [25]. In our study, 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 the age of onset of diabetes and the switch 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. 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 also be offered to the diabetic population.

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