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The Association of Smoking Status with Diabetic Microvascular Complications in Korean Patients with Type 2 Diabetes

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Purpose: Few studies have investigated the association between smoking and microvascular complications in the Asian population with type 2 diabetes mellitus (T2DM). We aimed to investigate the relationship between smoking status and microvascular complications in Korean patients with T2DM.

Materials and Methods: From the Korean National Diabetes Program cohort, we included 2316 Korean male with T2DM who had baseline clinical information available, including their smoking status, and underwent diabetic complication studies.

Results: Compared to non-smokers, current smokers had higher odds of any-microvascular complications [adjusted odds ratio (aOR) 1.45, 95% confidence interval (CI) 1.07–1.97, p=0.016]. The odds of neuropathy were significantly higher; however, the odds of retinopathy were significantly lower in current smokers than in nonsmokers (all p<0.05). Among those who underwent repeated complication tests after 3 years, the risk of newly developed retinopathy was significantly increased in ex-smokers [aOR 3.77 (95% CI 1.61–8.87), p=0.002]. Within ex-smokers, long smoking duration and smoking cessation within the recent 5 years were associated with an increased risk of newly developed retinopathy (all p<0.05).

Conclusion: Male smokers had higher odds of having overall diabetic microvascular complications, including neuropathy. However, the odds of having retinopathy were significantly lower among current smokers. More attention and research are needed regarding the increased risk of retinopathy development in ex-smokers who have recently stopped smoking after a long history of smoking.

Key Words: Smoking, diabetes complications, diabetic retinopathy, diabetic neuropathies

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INTRODUCTION

Patients with type 2 diabetes mellitus (T2DM) are at high risk of macrovascular and microvascular complications. Macrovascular complications, such as coronary heart disease, cerebrovascular disease, and peripheral vascular disease, significantly diminish the quality of life, often resulting in disability and an increased risk of premature death.[1] Concurrently, microvascular complications, principally represented by nephropathy, retinopathy, and neuropathy, also account for morbidity and impaired quality of life in people with diabetes.[1]

Cigarette smoking is one of the most important modifiable risk factors for cardiovascular diseases (CVD), accounting for 10% of all CVDs.[2] Smokers with T2DM have a 1.21 to 2.68-fold increased risk of CVD compared to non-smokers with T2DM.[3,4] The exact mechanism of how cigarette smoking is related to vascular disease is very complex due to the presence of approximately 4000 different chemicals in cigarettes. However, it is generally accepted that the generation of free radicals and oxidants through cigarette smoke is a probable mechanism underlying the close relationship between smoking and vascular diseases.[5,6]

Although smoking is an evident risk factor for CVD, whether it is also a risk factor for microvascular diseases, especially in individuals with diabetes, has long been questioned. Several studies have indicated that smoking is associated to an elevated risk of diabetic kidney disease and albuminuria in both type 1 diabetes mellitus (T1DM) and T2DM.[7-9] However, a recent meta-analysis concluded that smoking did not significantly increase the risk of developing diabetic kidney disease in patients with T2DM.[10] In addition, diabetic neuropathy was associated with smoking only in patients with T1DM, but not in those with T2DM.[11] Moreover, the effects of smoking on diabetic retinopathy remain more inconclusive. In some reports, diabetic retinopathy was not associated with smoking and was affected only by hyperglycemia.[12] In a meta-analysis, Cai, et al.[13] reported that the risk of diabetic retinopathy increased in smokers with T1DM and decreased in those with T2DM. These inconsistent results on the association between smoking and diabetic microvascular complications require further investigation. In the current study, we aimed to investigate the relationship between smoking and microvascular complications in Korean patients with T2DM.

MATERIALS AND METHODS

Study participants

The study participants were individuals enrolled in the Korean National Diabetes Program (KNDP) cohort. The KNDP cohort was a prospective, multicenter, observational cohort study that included patients with T2DM and those at high risk for diabetes. A total of 4324 patients were enrolled from 12 academic medical centers from May 2006 to December 2012 and followed up until March 2014. The details of the study cohort have been described previously (ClinicalTrials. gov Identifier: NCT01212198).[14] Patients who satisfied all of the following criteria were included in the analysis: 1) male aged over 20 years; 2) diagnosed with T2DM according to the American Diabetes Association criteria[15]; and 3) completed a self-questionnaire regarding their smoking status and underwent baseline clinical evaluation and complication studies. Female were excluded from the analysis since the proportions of female smokers and ex-smokers did not exceed 5% (2.8% and 3.9%, respectively). For additional analysis assessing the odds of developing of diabetic microvascular complications after a 3-year follow-up, we identified and analyzed the subgroups of patients who did not have microvascular complications at baseline. All the participants provided written informed consent, and this study was approved by the Ethics Committee of the Inha University Hospital (2022-10-019).

Clinical and laboratory measurements

The participants' demographics, anthropometrics, DM duration, smoking and alcohol status, history of cardiovascular or cerebrovascular disease, and baseline medications were collected using a self-reporting questionnaire. Smoking habits were classified into three categories: non-smokers, ex-smokers, and current smokers. Detailed information regarding smoking duration, average daily cigarette consumption, and the year of smoking cessation was also collected from current/ex-smokers. Alcohol consumption was classified into two categories: current regular drinking and non-drinking. Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg, or current use of antihypertensive medications. Hyperlipidemia was defined as low-density lipoprotein (LDL) ≥100 mg/dL or current use of statins. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Laboratory data, including the levels of glycated hemoglobin (HbA1c), total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, LDL-cholesterol, blood urea nitrogen, and creatinine, were measured using routine laboratory methods. The estimated glomerular filtration rate (eGFR) was assessed using the Modification of the Diet in Renal Disease equation.[16,17] Homeostatic model assessment of insulin resistance was performed using the following formula: fasting insulin (μU/mL)×fasting glucose (mg/dL)/40.[18]

Diabetic complications

Data on diabetic complications including nephropathy, neuropathy, and retinopathy were collected. Diabetic nephropathy was assessed through the Kidney Disease: Improving Global Outcomes guidelines, and was defined as patients with eGFR <60 mL/min/1.73 m^2 or the presence of albuminuria. The urine albumin-creatinine ratio was measured using a random urine sample, and albuminuria was defined as a UCAR of ≥30 μg/mg Cr.[19] Diabetic retinopathy was assessed through color fundus photography and diagnosed according to the Early Treatment Diabetic Retinopathy Study criteria.[20] The diagnosis of diabetic neuropathy was based on the presence of any of the following three criteria: 1) symptoms of neuropathy, 2) signs of neuropathy, or 3) confirmation using a nerve conduction test. Neuropathy symptoms were assessed using a self-reported questionnaire based on the Diabetic Neuropathy Symptom score,[21] while signs of neuropathy were evaluated using the Diabetic Neuropathy Examination score.[22] Any microvascular complication was defined as the presence of one or more confirmed complications in patients who had undergone one or more

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studies related to complications. Among the patients without any complications, those who did not undergo all three tests (nephropathy, neuropathy, and retinopathy) were excluded from the analysis related to any microvascular complications. Newly developed diabetic complications were evaluated for retinopathy and nephropathy, defined as the detection of these complications in repeated studies at the 3-year follow-up.

Statistical analysis

The baseline characteristics of the study participants were analyzed according to their current smoking status. The patients were divided into three groups: non-smokers, ex-smokers, and current smokers. Data were presented as mean±standard deviation or as numbers (percentages) for categorical variables. Continuous variables were analyzed using one-way analysis of variance for intergroup comparisons, followed by the Bonferroni test for post-hoc analysis. All categorical variables were expressed as numbers (proportions) and compared using the χ^2 test.

Multiple logistic regression analysis was performed to evaluate the statistical significance of the baseline odds of diabetic complications and the risk of newly developed diabetic complications at the 3-year follow-up in the study groups. Various confounding factors were sequentially adjusted for age, BMI, HbA1c, DM duration, presence of hypertension, dyslipidemia, CVD and cerebrovascular disease, diabetes medication, and alcohol consumption. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. Statistical analysis was performed using IBM SPSS statistical software for Windows (version 26.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $p<0.05$.

Table 1. Baseline Characteristics of Study Participants (n=2316)

	Non-smoker (n=549)	Ex-smoker (n=924)	Current smoker (n=843)	*p* value
Age, yr	53.5±11.3	53.9±9.7	49.4±9.3*†	<0.001
Body weight, kg	70.0±10.5	71.1±10.0	72.2±10.7*	<0.001
BMI, kg/m^2	25.0±3.1	25.0±2.9	25.0±3.0	0.929
Waist circumference, cm	88.7±8.3	89.5±7.6	89.4±7.4	0.135
Systolic BP, mm Hg	126.6±15.2	125.9±14.6	125.3±14.4	0.289
Diastolic BP, mm Hg	78.6±9.7	78.9±9.7	79.2±9.8	0.541
Duration of diabetes, yr	6.5±6.7	5.6±6.4*	5.3±5.9*	0.002
HbA1c, %	7.9±1.9	7.9±1.9	8.2±2.1*†	<0.001
HOMA-IR	2.9±2.4	3.3±5.1	3.5±4.8	0.105
Fasting glucose	150.6±54.2	149.1±50.4	158.7±62.5*	0.001
Glucose, 2PC	277.1±99.5	266.9±104.6	287.4±110.6	0.001
Total cholesterol, mg/dL	178.5±40.2	179.6±40.7	182.1±40.9	0.228
Triglyceride, mg/dL	151.7±144.7	165.6±133.4	191.8±134.2*†	<0.001
HDL-cholesterol, mg/dL	47.3±11.9	46.1±12.0	45.0±11.6*	0.003
LDL-cholesterol, mg/dL	102.6±34.3	101.9±35.3	100.9±35.8	0.681
eGFR-MDRD, mL/min/1.73m^2	92.5±32.5	95.8±29.3	104.3±31.4*†	<0.001
Diabetes medications				0.390
Without medication	64/488 (13.1)	106/820 (12.9)	99/749 (13.2)	
OAD(s) only	334/488 (68.4)	565/820 (68.9)	489/749 (65.3)	
Insulin only	32/488 (6.6)	70/820 (8.5)	67/749 (8.9)	
OADs plus insulin	58/488 (11.9)	79/820 (9.6)	94/749 (12.6)	
Alcohol consumption, current	296/543 (54.5)	649/919 (70.6)	662/840 (78.8)	<0.001
Hypertension	290/549 (52.8)	505/924 (54.7)	415/843 (49.2)	0.071
Hyperlipidemia	344/549 (62.7)	567/924 (61.4)	523/843 (62.0)	0.881
Previous cardiovascular disease	34/549 (6.2)	91/924 (9.8)	64/843 (7.6)	0.035
Previous cerebrovascular disease	30/549 (5.5)	57/924 (6.2)	39/843 (4.6)	0.361
Any micro-complications	295/421 (70.1)	528/723 (73.0)	479/633 (75.7)	0.130
Diabetic neuropathy	193/466 (41.4)	372/820 (45.4)	338/727 (46.5)	0.212
Diabetic retinopathy	115/417 (27.6)	156/754 (20.7)	125/637 (19.6)	0.005
Diabetic nephropathy	148/549 (27.0)	220/924 (23.8)	218/843 (25.9)	0.363

BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study; OAD, oral antidiabetic drug. Data are presented as mean±standard deviation or n/total (%).
*$p<0.05$, vs. non-smoker, by post hoc analyses (Bonferroni test); †$p<0.05$, vs. ex-smoker, by post hoc analyses (Bonferroni test).

RESULTS

The baseline characteristics of the study participants are shown in Table 1. Of the 2316 patients with T2DM, 843 (36.4%) were current smokers and 924 (39.9%) were ex-smokers. The mean age of current smokers was 49.4±9.3 years, which was significantly lower compared to other groups (p<0.001). The HbA1c level (%) was higher in current smokers (8.2±2.1) compared to non-smokers (7.9±1.9) and ex-smokers (7.9±1.9) (p=0.003 and p<0.001, respectively). Current smokers had a shorter duration of diabetes (5.3±5.9 years) compared to non-smokers (6.5±6.7 years) (p=0.002). Triglyceride level (mg/dL) was higher in current smokers (191.8±134.2) compared to non-smokers (151.7±144.7) and ex-smokers (165.6±133.4) (all p<0.001). HDL-cholesterol level (mg/dL) was lower (45.0±11.6) in current smokers compared to non-smokers (47.3±11.9) (p=0.002). There were no significant differences in the use of medications for diabetes among the groups. However, the proportion of participants with current alcohol consumption was the highest among current smokers and lowest among non-smokers (p<0.001).

The odds of having microvascular complications in ex-smokers and current smokers was compared to that in non-smokers (Table 2). Current smoking was associated with increased odds of having any microvascular complications (aOR 1.45, 95% CI 1.07–1.97). The odds of diabetic neuropathy were significantly higher in current smokers (aOR 1.38, 95% CI 1.05–1.81). In contrast, the odds of diabetic retinopathy were inversely associated with current smoking (aOR 0.62, 95% CI 0.44–0.88).

For patients who did not have any complications at the initial evaluation, we further assessed the relationship between smoking status at baseline and the development of retinopathy or nephropathy after a 3-year follow-up period (Table 3). Ex-smokers had increased odds of developing diabetic retinopathy (aOR 3.77, 95% CI 1.61–8.87). However, current smokers did not have an increased risk of retinopathy (aOR 2.19, 95% CI 0.85–5.70). The development of nephropathy was not found to be associated with smoking status at baseline.

The associations between other clinical parameters and the development of retinopathy in ex-smokers were analyzed (Supplementary Table 1, only online). Smoking duration was positively associated with increased risk of retinopathy in ex-smokers (OR 1.04, 95% CI 1.01–1.08). Notably, participants who stopped smoking within the past 5 years were associated with an increased risk of retinopathy (OR 2.07, 95% CI 1.09–3.92) (Supplementary Table 2, only online).

Table 2. Odds Ratio of Having Diabetic Microvascular Complications in Patients with T2DM according to Smoking Status

	Ex-smoker	p value	Current smoker	p value
	aOR (95% CI)		aOR (95% CI)	
Any-micro (n=1618)				
Model 1	1.12 (0.85–1.47)	0.428	1.42 (1.06–1.89)	0.017
Model 2	1.17 (0.89–1.55)	0.261	1.42 (1.06–1.90)	0.019
Model 3	1.20 (0.92–1.57)	0.169	1.43 (1.08–1.89)	0.011
Model 4	1.18 (0.89–1.58)	0.251	1.45 (1.07–1.97)	0.016
Neuropathy (n=1691)				
Model 1	1.19 (0.93–1.53)	0.172	1.40 (1.08–1.83)	0.012
Model 2	1.23 (0.95–1.59)	0.111	1.42 (1.09–1.85)	0.010
Model 3	1.27 (1.00–1.61)	0.052	1.41 (1.10–1.81)	0.007
Model 4	1.23 (0.95–1.59)	0.124	1.38 (1.05–1.81)	0.021
Retinopathy (n=1574)				
Model 1	0.64 (0.48–0.86)	0.003	0.68 (0.49–0.94)	0.018
Model 2	0.69 (0.50–0.94)	0.019	0.64 (0.45–0.89)	0.008
Model 3	0.74 (0.55–1.00)	0.053	0.68 (0.49–0.94)	0.020
Model 4	0.67 (0.48–0.92)	0.014	0.62 (0.44–0.88)	0.008
Nephropathy (n=1960)				
Model 1	0.81 (0.62–1.05)	0.117	0.87 (0.75–1.29)	0.909
Model 2	0.84 (0.64–1.10)	0.208	1.00 (0.76–1.32)	0.980
Model 3	0.86 (0.66–1.11)	0.244	1.09 (0.84–1.42)	0.527
Model 4	0.85 (0.64–1.12)	0.235	1.04 (0.78–1.38)	0.817

T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycated hemoglobin; DM, diabetes mellitus.
Model 1=age; Model 2=Model 1+BMI, HbA1c and DM duration; Model 3=Model 2+history of hypertension, dyslipidemia, cardiovascular disease, and cerebrovascular disease; Model 4=Model 3+diabetes medication and alcohol consumption were adjusted.

DISCUSSION

In this study, we found that smokers with T2DM were at increased odds of having diabetic microvascular complications, including neuropathy, compared to non-smokers with T2DM. The odds of having diabetic retinopathy showed inverse results; smokers had lower odds of developing retinopathy compared to non-smokers. Interestingly, patients who quit smoking within the past 5 years after a long history of smoking had an increased risk of retinopathy development.

Smoking is associated with several unfavorable health outcomes, and researchers have focused on vascular complica-

Table 3. Odds Ratio of New Development of Diabetic Microvascular Complications after 3 Years in Patients with T2DM according to Smoking Status

	Ex-smoker	p value	Current smoker	p value
	aOR (95% CI)		aOR (95% CI)	
Retinopathy (n=631)				
Unadjusted	3.13 (1.38–7.14)	0.007	1.70 (0.69–4.23)	0.252
Adjusted	3.77 (1.61–8.87)	0.002	2.19 (0.85–5.70)	0.105
Nephropathy (n=755)				
Unadjusted	1.42 (0.52–3.89)	0.499	1.28 (0.44–3.75)	0.656
Adjusted	1.29 (0.46–3.60)	0.631	1.04 (0.34–3.15)	0.945

T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycated hemoglobin; DM, diabetes mellitus.
Age, BMI, HbA1c, DM duration, history of hypertension, dyslipidemia, cardiovascular disease and cerebrovascular disease, diabetes medication, and alcohol consumption were adjusted.

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tions in smokers with T2DM. The risk of macrovascular complications, such as myocardial infarction and stroke, is notably higher in smokers.[23] In several previous studies, diabetic microvascular complications, such as neuropathy and nephropathy, were more prevalent in smokers than in nonsmokers.[8,11] However, the findings regarding these associations have been inconsistent across studies, and most of the existing evidence is derived from cross-sectional designs, limiting the ability to establish a causal relationship between smoking and microvascular complications.

Several cross-sectional studies have investigated the association between diabetic neuropathy and smoking. Mitchell, et al.[11] conducted a study involving patients with T1DM and found that those who smoked 30 pack-years or more had a 3.32-fold higher risk of diabetic neuropathy compared to those who smoked less. However, this increased risk of diabetic neuropathy was not observed in smokers with T2DM.[11] Additionally, a meta-analysis showed that smoking did not increase the risk of diabetic neuropathy.[24] In contrast, in a prospective study by Tesfaye, et al.,[25] smoking was identified as a risk factor for diabetic neuropathy. Furthermore, in a recent study that included 15352 patients with T1DM or T2DM, current smokers had a 1.54-fold higher risk of developing peripheral neuropathy.[26] Similarly, in our study, current smokers had a 1.42-fold increased odds of having diabetic neuropathy. Several potential mechanisms have been suggested for the development of diabetic neuropathy in smokers. Cigarette smoke is a source of free radicals and oxidants that induce oxidative stress in the nervous system, leading to cellular damage and apoptosis.[5,6] In addition, smoking inhibits insulin signaling and induces advanced glycation end products, which cause oxidative stress, mitochondrial dysfunction, and deoxyribonucleic acid damage.[5,6]

However, the association between smoking and retinopathy is far more controversial. Unlike the risk of other diabetic complications, the risk of diabetic retinopathy has been reported to decrease in smokers, which contradicts the general concept of the hazardous effects of smoking. In the United Kingdom Prospective Diabetes Study, current smokers were associated with reduced incidence of retinopathy, showing a relative risk of 0.63 (95% CI 0.48–0.82).[27] Gange, et al.[28] reported the computed incidence of proliferative diabetic retinopathy 5 years after the diagnosis of T2DM, and smoking was identified as a protective factor (OR 0.84, 95% CI 0.70–1.00). A recent meta-analysis also showed that the risk of diabetic retinopathy was significantly lower in smokers with T2DM.[13] Consistent with previous studies, this study showed that current smokers had a lower odds of having diabetic retinopathy compared to non-smokers. Additionally, ex-smokers who had stopped smoking within the last 5 years had a significantly higher risk of developing new retinopathy. Although these results may indicate that smoking plays a protective role against diabetic retinopathy, it is difficult to conclude. Evidence supporting the protective role of smoking is still lacking. Previous studies have attempted to elucidate the underlying mechanisms leading to these counterintuitive findings. The BP-lowering effect and other pharmacological effects of smoking tobacco, such as nicotine, have been suggested as plausible mechanisms underlying the reduced risk of diabetic retinopathy.[27] However, none of these reports have been conclusive and no further evidence has been revealed. Furthermore, in a meta-analysis by Cai, et al.,[13] a decreased risk of diabetic retinopathy was observed only in smokers with T2DM, while the risk of retinopathy was significantly increased in smokers with T1DM. This disparity in the association between smoking and T1DM or T2DM is not well understood.

In the current study, patients who stopped smoking had increased odds of developing diabetic retinopathy. However, regarding the general harmful effects of cigarette smoking on health, this finding does not advocate for continuing smoking. Moreover, participants who continued to smoke during the 3-year follow-up also had increased odds of developing retinopathy, although the difference was not statistically significant. Even in studies which included patients with T2DM, the association between smoking and retinopathy is not firmly established. In a recent study by Park, et al.,[29] smoking was not associated with diabetic retinopathy. On the contrary, smoking was an independent risk factor for retinal neovascularization of diabetic retinopathy and it impaired retinal microcirculation in patients with T2DM,[30,31] suggesting that smoking potentially plays a role in the pathogenesis of diabetic retinopathy.

Smokers with diabetes have been reported to have a higher risk of proteinuria and low GFR. Smoking is related to the development of microalbuminuria,[32,33] progression from microalbuminuria to macroalbuminuria,[34] and progression from early stage nephropathy to end-stage renal disease[9,35]; however, the mechanism by which smoking is related to reduced renal function is not fully understood. Tobacco has been suggested to impair the structure and function of the glomeruli.[36] Additionally, heavy metals generated by smoking may accumulate in the blood and cause damage to the glomeruli.[37] Histopathological finding of the kidneys of smokers showed mesangial expansion and renal arteriolar hyalinization, which implicated glomerular damage and altered renal function.[38] However, in this study, we did not observe an increased odds of having nephropathy in smokers with T2DM. One meta-analysis concluded that smoking does not significantly increase the risk of developing diabetic kidney disease in individuals with type 2 diabetes.[11] In another meta-analysis that reported a significant association between smoking and the development of albuminuria, five out of the 13 studies included in the analysis did not show a significant increase in the odds of developing albuminuria in smokers.[39] This suggests that the association between nephropathy and smoking in patients with type 2 diabetes may not be very strong.

The present study has several strengths. This study was based on cohort results from 12 tertiary hospitals in Korea. Various factors, including smoking status, were evaluated using a uni-

fied method, and multiple microvascular complications were simultaneously evaluated. In addition, we analyzed the 3-year follow-up data and investigated the role of smoking in the development of new-onset diabetic microvascular complications. However, this study also has several limitations. First, female smokers with T2DM were not included. Female were excluded as their smoking rate was low in the KNDP database, and meaningful comparative analysis was difficult. Therefore, the results of our study cannot be generalized to female. Second, the categorization of participants into non-smokers, ex-smokers, and current smokers, while useful for broad comparisons, may overlook the potential impact of factors such as smoking duration and cumulative smoking amount. Unfortunately, due to the study design, we were unable to adequately capture and account for individual variations in these smoking characteristics. Third, the assessment for neuropathy was not consistently conducted by the same evaluator or equipment, introducing the possibility of variations in the identification of comorbidities across patients and institutions. In addition, major analysis was conducted using cross-sectional data, limiting our ability to infer causal relationships and allowing us to discuss only associations.

In this study, smoking was associated with increased odds of having microvascular complications. When analyzed for each complication, the odds ratio of diabetic neuropathy was significantly higher in current smokers. The odds ratio for diabetic retinopathy was lower in current smokers than in non-smokers. Considering that ex-smokers with a long history of smoking were at a high risk of newly developed retinopathy, more attention is needed on the increased risk of retinopathy development in ex-smokers, especially those who have recently quit smoking. Further research is required to investigate the mechanisms underlying the association between smoking and microvascular complications.

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AUTHOR CONTRIBUTIONS

Conceptualization: Yongin Cho and So Hun Kim. Data curation: Yongin Cho, Hye-Sun Park, Da Hea Seo, Seong Hee Ahn, Seongbin Hong, and Young Ju Suh. Formal analysis: Yongin Cho and Hye-Sun Park. Funding acquisition: Yongin Cho and So Hun Kim. Investigation: Yongin Cho and Hye-Sun Park. Methodology: Yongin Cho, Hye-Sun Park, Da Hea Seo, Seong Hee Ahn, Seongbin Hong, Young Ju Suh, Suk Chon, Jeong-Taek Woo, Sei Hyun Baik, and Kwan Woo Lee. Project administration: Yongin Cho, Suk Chon, Jeong-Taek Woo, Sei Hyun Baik, Kwan Woo Lee, and So Hun Kim. Resources: Yongin Cho, Suk Chon, Jeong-Taek Woo, Sei Hyun Baik, Kwan Woo Lee, and So Hun Kim. Software: Yongin Cho and Young Ju Suh. Supervision: Yongin Cho and So Hun Kim. Validation: Yongin Cho, Hye-Sun Park, and So Hun Kim. Visualization: Yongin Cho, Hye-Sun Park, and So Hun Kim. Writing—original draft: Yongin Cho and Hye-Sun Park. Writing—review & editing: Yongin Cho, Hye-Sun Park, and So Hun Kim. Approval of final manuscript: all authors.

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