Journal of
Oral Health and Oral Epidemiology

https://johoe.kmu.ac.ir
10.34172/johoe.2410.1691
JOHOE. 2025;14:2410.1691

Original Article

The relationship between diabetes mellitus and oral lesions: A cross-sectional study based on cohort data of Adults in Southeastern Iran

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Abstract

Background: Our study investigated the relationship between the prevalence of oral lesions and diabetes mellitus (DM) in Rafsanjan, located in southeastern Iran.

Method: This cross-sectional study drew upon baseline data from the Oral Health Branch of Rafsanjan Cohort Study (OHBRCS), a component of the broader Rafsanjan Cohort Study (RCS). The RCS, initiated in 2015 in Rafsanjan, is an ongoing prospective epidemiological investigation within the framework of the Prospective Epidemiological Research Studies in Iran (PERSIAN), with follow-up phases currently in progress. Thorough oral examinations were performed by trained dental professionals, who identified oral lesions through clinical assessment. Data concerning DM was collected from participants' self-reported medical histories, subsequently corroborated by a physician. To assess the association between DM and oral lesions, both univariate and multivariate dichotomous logistic regression analyses were conducted.

Results: Of the 8640 participants examined (mean age=49.95 years), 1698 (19.65%) individuals were diagnosed with DM. The study also identified the prevalence of several oral conditions, encompassing diffuse oral pigmentation (13.91%), non-diffuse pigmentation (11.5%), candidiasis (10.42%), red and white lesions (8.24%), leukoplakia (7.48%), herpes (5.06%), oral exophytic lesions (4.48%), and erythroplakia (0.94%). In an adjusted analysis, DM was correlated with a reduced probability of diffuse oral pigmentation (odds ratio [OR]: 0.8; 95% confidence interval [CI]: 0.69-0.95). Additionally, within the same adjusted model, diabetic patients receiving insulin therapy demonstrated a significantly elevated likelihood (6.63 times) of developing erythroplakia when contrasted with those not undergoing insulin therapy (OR: 6.63; 95% CI: 1.23-36.26).

Conclusion: Diabetic patients exhibited a reduced incidence of diffuse oral pigmentation. Conversely, erythroplakia was observed more frequently in diabetic patients undergoing insulin therapy. Further long-term investigations are necessary to substantiate these preliminary findings.

Keywords: Diabetes mellitus, Oral candidiasis, Erythroplakia, Leukoplakia, Oral pigmentation, Oral Health Branch of Rafsanjan Cohort Study

Citation: Rezvaninejad R, Ahmadi F, Jamali Z, Khalili P, Sardari F, Behzadifar H, et al. The relationship between diabetes mellitus and oral lesions: a cross-sectional study based on cohort data of adults in Southeastern Iran. *J Oral Health Oral Epidemiol*. 2025;14:2410.1691. doi:10.34172/johoe.2410.1691

Received: October 15, 2024, **Accepted:** February 18, 2025, **ePublished:** July 8, 2025

Introduction

Diabetes mellitus (DM) is an umbrella term for a cluster of disorders characterized by elevated blood glucose levels, which stem from either insufficient insulin production or increased cellular resistance to insulin's actions. Consequently, DM culminates in diverse metabolic disruptions affecting the processing of carbohydrates, fats, and proteins.[1]

Type 2 DM (T2DM), historically referred to as adult-onset diabetes, accounts for over 95% of all DM cases.

This condition is characterized by the body's diminished capacity to effectively utilize insulin.[2] Consequently, DM significantly impacts an individual's health-related quality of life. DM, recognized as a leading chronic condition globally, significantly contributes to worldwide mortality rates.[3] Historically associated with Western lifestyles, DM has had a more rapid increase in prevalence in recent years, particularly in low- and middle-income nations compared to high-income countries.[4]

In 2017, the global prevalence of DM was substantial, affecting either 424.9 million individuals aged 20-79 or 451 million individuals aged 18-99. Projections indicate a significant increase in these figures by 2045, with estimates rising to 629 million and 693 million, respectively. A comparison with the 2000 publication of the International Diabetes Federation (IDF) Diabetes Atlas reveals that the 2017 estimate for the 20-79 age group is 28.1% higher than previously projected. The 2000 Atlas had anticipated a global DM rate of 7.7% by 2030. Furthermore, between 2010 and 2030, a disproportional increase in DM prevalence is expected, with a 69% rise in developing countries, such as Iran, compared to a 20% rise in developed nations.[5]

DM is associated with a wide range of oral complications,[6] encompassing xerostomia, root caries, periapical lesions, gingivitis, periodontiti, oral fungal infections (candidiasis), glossodynia, burning mouth syndrome, geographic tongue, fissured tongue, coated tongue, oral lichen planus (OLP),[7] recurrent mouth ulcers (aphthous stomatitis), herpes ulcers, an increased risk of infections, and delayed wound healing, as well as premalignant conditions, such as leukoplakia and erythroplakia.[8] Diabetic patients often present with alterations in oral pigmentation, which can manifest as melanin pigmentation or other types of discoloration. These changes are frequently associated with the underlying DM-related metabolic conditions. A comprehensive understanding of these diverse oral health manifestations is paramount for developing effective management and prevention strategies for diabetic individuals, given their substantial impact on overall health and quality of life.[9] Proper oral hygiene and regular dental check-ups are essential for such individuals to minimize adverse effects and maintain good oral health.[10] Oral health professionals are particularly concerned about the potential impacts of DM on various oral conditions.[2] The severity of clinical signs and oral symptoms observed in diabetic individuals can vary significantly from mild to more severe. Such variability is contingent upon several factors: The specific classification of the hyperglycemic disorder, the efficacy of disease management strategies, and the duration since the initial diagnosis of the condition.[11]

For individuals with DM, it is essential for healthcare professionals to possess a thorough understanding of oral lesion diagnosis. This is because numerous factors can influence the oral health of patients with DM.[12] Accurate diagnosis, appropriate prescription, and effective treatments are paramount to minimizing complications and improving the patient's overall quality of life.[11]

As shown by D'Aiuto et al DM has been linked to a range of oral health issues, including specific effects on oral health, notably an elevated risk of periodontitis, an increased likelihood of developing oral cancer, and potential implications for the long-term success of dental implants among individuals in the UK.[13] Ponte et al indicated that diabetic individuals exhibited an increased susceptibility to stomatitis and glossitis. Although some contradictory findings exist, a significant association appears to be present between DM and OLP, particularly its erosive form.[14] Additionally, Farrasoya et al conducted a review focusing on recent discoveries concerning oral manifestations in diabetic patients, with a particular emphasis on alterations in soft tissues and their implications for treatment strategies.[15] Separately, Sanjeeta et al reported a significant correlation between DM-related xerostomia and the presence of chronic periodontitis; however, their study showed no notable associations between DM-related xerostomia and other categories of oral lesions.[16]

Compared to the extensive research on dental caries and periodontal diseases, studies on oral mucosal lesions are less common globally. Nevertheless, existing data indicate a higher prevalence of these lesions in diabetic compared to non-diabetic individuals.[16] This study aimed to investigate the relationship between oral lesions and T2DM, thereby contributing novel perspectives to the current academic discourse.

Methods

Study Design and Patient Selection

This cross-sectional study drew upon data from the initial phase of the Oral Health Branch of Rafsanjan Cohort Study (OHBRCS).[17] The OHBRCS, in turn, was initiated as part of the broader Rafsanjan Cohort Study (RCS), with its primary objective being the investigation of crucial aspects of dental and oral health among the study participants. The RCS commenced in August 2015 in Rafsanjan, located in southeastern Iran.[17] The initial data collection phase concluded in December 2017, with a minimum five-year follow-up period planned. A total of 9,991 individuals (age range = 35-70 years) voluntarily enrolled in the study after providing written informed consent. This study was conducted in accordance with the Prospective Epidemiological Research Studies in Iran (PERSIAN) protocol[18] and received ethical approval from the Ethics Committee of Rafsanjan University of Medical Sciences (IR.RUMS.REC.1401.216). Additionally, the research design and execution followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data Collection

Data on participants' demographic and socioeconomic status (SES), treatment regimens, medical history, lifestyle behaviors, and anthropometric measurements were collected using validated electronic questionnaires.[17]

Self-reported behaviors encompassed opium use, cigarette smoking, and alcohol use. Participants qualified as current smokers if they had consumed more than 100 cigarettes over their lifetime and reported ongoing smoking. Individuals who had previously smoked more than 100 cigarettes but had ceased smoking were categorized as former smokers. Participants were identified as opium users if they reported weekly opium use for at least six months.[19] Alcohol use was defined as the consumption of approximately 200 mL of beer or 45 mL of spirits per week for at least six months.[20]

Participants' SES was assessed using the Wealth Score Index (WSI). Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared) and categorized into three groups: $BMI < 25$; $25.0 \leq BMI < 30$; and $BMI \geq 30$.

From the original RCS adult cohort, 8,682 participants were recruited for the OHBRCS. After excluding individuals with incomplete medical history data, specifically concerning DM, 8,640 participants were ultimately included in the present study.

Oral data were gathered via interviewer-administered questionnaires designed to capture almost all aspects of a thorough dental and intraoral assessment. A trained dentist performed a comprehensive clinical oral examination on every participant in the study. To ensure a comprehensive assessment of the oral mucosa, dental mirrors, tongue depressors, and flashlights were employed. A meticulous examination was conducted on the oral mucosa, vestibule, alveolar ridges, dorsal and ventral surfaces, lateral edges of the tongue, floor of the mouth, hard and soft palate, mucosal surfaces of the upper and lower lips, and gingiva to detect any oral mucosal lesions.

In this study, a range of oral lesions observed in patients were investigated. These lesions consisted of oral mucosal lesions like white and red plaques (candidiasis), ulcers (herpes), various forms of oral pigmentation (both diffuse and non-diffuse), oral exophytic lesions, leukoplakia, and erythroplakia. The diagnosis of these lesions relied exclusively on clinical presentation, as laboratory investigations were not performed.[21] The initial diagnoses were subsequently validated by a consensus of three oral medicine specialists to guarantee accuracy. Toothbrushing practices were stratified into two categories: Individuals who brushed their teeth and those who did not.

When discussing candidiasis, it is crucial to recognize its diverse clinical presentations, including pseudomembranous candidiasis (thrush), erythematous candidiasis, and angular cheilitis. Each of these forms exhibits distinct clinical characteristics and, consequently, necessitates individualized management approaches.[22] Moreover, the research examined how dentures affect oral health, noting their potential to foster oral lesion development, especially in diabetic patients. Dentures can foster environments conducive to fungal infections, such as candidiasis, which underscores the importance of rigorous oral hygiene for those who wear them.[23] In the current research, individuals utilizing dentures (either partial or complete) were categorized as denture users. The denture use duration was subsequently classified into three distinct groups: Less than 1 year, 1-5 years, and exceeding 5 years.

In this study, individuals with a physician-confirmed diagnosis of DM were designated to the diabetic group. DM treatment regimens were systematically stratified into four distinct categories: No treatment, insulin therapy, oral medications (pills), and a combination of both insulin therapy and pills. This classification facilitates a thorough examination of the potential impact of various therapeutic approaches on the prevalence of oral lesions within the diabetic patient population.

Statistical Analyses

We calculated frequency percentages for categorical variables, and the mean and standard deviation for quantitative variables. We then compared these baseline characteristics across the different study groups. Chi-square (χ^2) tests were used for categorical variables, and t-tests were employed for continuous variables. To investigate the relationship between DM and oral lesions among the study participants, we performed both univariate and multivariate dichotomous logistic regression analyses. These analyses allowed us to determine the odds ratios (ORs) and their respective 95% confidence intervals (CIs). In the regression analysis, we employed two distinct models: A crude model and an adjusted model. Variables demonstrating a p-value of less than 0.25 in the preliminary bivariate analysis were considered for inclusion in the regression models as potential confounders. The crude model underwent stratification based on DM status. Conversely, the adjusted model systematically controlled for several confounding variables, including age, education, WSI, BMI, gender, personal behaviors, denture use duration, and brushing habits.

Results

Table 1 summarizes the participants' general characteristics, personal and oral habits, anthropometric measurements, and DM treatment modalities. Of the 8,640 individuals in this study, 6,941 (80.35%) were non-diabetic, while 1,698 (19.65%) were diabetic patients. In the cohort of diabetic patients, women constituted a larger proportion of diabetic individuals compared to men (22.62% versus 16.21%; mean age = 49.95 ± 9.50

Table 1. Demographic, selected medical and laboratory characteristics of study participants (n = 8640)

Characteristics	All (n = 8640)	Non-Diabetes (n = 6941)	Diabetes (n = 1698)	*P* Value
Age- years. No. (%)				< 0.001
35-45	3195(36.98)	2977(93.18)	218(6.82)	
46-55	2698(30.83)	2150(80.01)	537(19.99)	
≥ 56	2757(32.06)	1814(65.80)	943(34.20)	
Mean ± SD	49.95 ± 9.50	48.54 ± 9.26	55.73 ± 8.19	< 0.001
Gender- No. (%)				< 0.001
Female	4642(53.73)	3592(77.38)	1050(22.62)	
Male	3998(46.27)	3350(83.79)	648(16.21)	
Education-No. (%)				< 0.001
≤ 5 years	2960(34.28)	2144(72.43)	816(27.57)	
6-12 years	4216(48.82)	3523(83.56)	693(16.44)	
≥ 13 years	1459(16.90)	1270(87.05)	189(12.95)	
BMI- No. (%)				< 0.001
Mean ± SD	27.86 ± 4.84	27.57 ± 4.08	29.09 ± 4.80	
WSI- No. (%)				< 0.001
Mean ± SD	0.354 ± 0.981	0.0679 ± 0.980	-.0974 ± 0.976	
Alcohol use- No. (%)				< 0.001
Yes	857(9.93)	752(87.75)	105(12.25)	
No	7770(90.07)	6178(79.51)	1592(20.49)	
Cigarette smoking-No. (%)				< 0.001
Current	1396(16.18)	1203(86.17)	193(13.83)	
Never	6481(75.12)	5135(79.23)	1346(20.77)	
Former	750(8.6)	592(78.93)	158(21.07)	
Opium use- No. (%)				0.016
Yes	1954(22.65)	1067(82.24)	347(17.26)	
No	6673(77.35)	5323(79.77)	1350(20.23)	
Brushing- No. (%)				< 0.001
Yes	6132(70.97)	5068(82.65)	1064(17.35)	
No	2508(29.3)	1824(74.72)	634(25.28)	
Denture- No. (%)				< 0.001
Yes	2852(33.91)	2083(73.04)	769(26.96)	
No	5559(66.09)	4669(83.99)	890(16.01)	
Denture duration- No. (%)				0.001
< 1 year	146(5.12)	113(5.43)	33(4.29)	
1-5 years	822(28.84)	638(30.66)	184(23.93)	
> 5 years	1863(65.37)	1319(63.38)	544(70.74)	
Treatment type in diabetic subjects (n = 1698)				
Insulin therapy		106(6.24)		
Pills		907(53.42)		
Insulin therapy + pills		99(5.83)		
No treatment		586(34.51)		
DM duration in diabetic subjects (n = 1698)				
Mean ± SD (year)		6.07 ± 1.26		

SD: Standard deviation; BMI: Body mass index; WSI: Wealth Score Index; DM: Diabetes mellitus

years). Notably, diabetic participants were significantly older than individuals in the control group (mean age = 55.73 ± 8.19 versus 48.54 ± 9.26 years). Furthermore, diabetic individuals presented with a higher BMI and a

lower WSI. Regarding lifestyle characteristics, 12.25% of individuals reported alcohol use, while 13.83% were identified as current cigarette smokers. Opium use was reported by 17.26% of subjects, 26.96% wore dentures, and 17.35% engaged in regular tooth brushing practices. In terms of DM management, the distribution of treatment types among diabetic patients was as follows: 34.51% received no treatment, 6.24% were on insulin therapy, 53.42% managed their condition with pills, and 5.83% used both insulin therapy and pills. The mean DM duration in this population was 6.07 ± 1.26 years.

Table 2 presents a detailed breakdown of the prevalence of various oral lesions observed in both diabetic and non-diabetic individuals. The findings indicated the following frequencies: Diffuse oral pigmentation (13.91%), non-diffuse oral pigmentation (11.5%), candidiasis (10.42%), red and white lesions (8.24%), leukoplakia (7.48%), herpes (5.06%), oral exophytic lesions (4.48%), and erythroplakia (0.94%). Diabetic patients exhibited a significantly lower prevalence of diffuse oral pigmentation compared to non-diabetic patients (13.91% versus 21.96%). Conversely, oral candidiasis was observed significantly more frequently in diabetic individuals than in their non-diabetic counterparts (10.42% versus 7.32%). The prevalence of other oral lesions showed no statistically significant differences between the two groups.

Table 3 presents the relationships between oral lesions and DM, as analyzed through regression models. The crude model indicated that diabetic individuals had lower odds of diffuse oral pigmentation (OR: 0.57; 95% CI: 0.49–0.67). This significant association persisted even after adjusting for confounding variables (OR: 0.82; 95% CI: 0.7–0.97). In the unadjusted model, diabetic individuals exhibited statistically significant increased odds of developing oral candidiasis (OR: 1.47; 95% CI: 1.23–1.76). However, this association ceased to be significant after adjusting for confounding variables. No other significant relationships were found between DM and other oral lesions examined.

Table 4 illustrates the relationships between treatment type, DM duration, and the prevalence of oral lesions in diabetic participants, as analyzed through regression models. Specifically, the crude model indicated that diabetic patients undergoing insulin therapy had 5.6 times higher odds of developing erythroplakia compared to those not receiving treatment (OR: 5.66; 95% CI: 1.21–28.42). This significant association persisted even after adjusting for confounding factors (OR: 6.8; 95% CI: 1.23–37.45). Following adjustment, the insulin therapy group demonstrated a marginally significant reduction

Table 2. The prevalence of oral lesions among study participants according to diabetes mellitus history (n = 8640)

Oral Diseases	All (n = 8640)	Non-Diabetes (n = 6941)	Diabetes (n = 1698)	*P* Value
Diffuse oral pigmentation				<0.001
Yes	1759(20.38)	1523(21.96)	236(13.91)	
No	6872(79.62)	5411(78.4)	1461(86.09)	
Non diffuse oral pigmentation				0.549
Yes	956(11.09)	761(10.99)	195(11.50)	
No	7666(88.91)	6165(89.01)	1501(88.50)	
Oral exophytic lesions				
Yes	358(4.15)	282(4.07)	76(4.48)	0.449
No	8624(95.85)	6644(95.93)	1620(95.52)	
Herpes				
Yes	377(4.36)	291(4.19)	86(5.06)	0.114
No	8236(95.64)	6651(95.81)	1612(94.94)	
Erythroplakia				
Yes	76(0.88)	60(0.86)	16(0.94)	0.75
No	8546(99.12)	6882(99.14)	1682(99.06)	
Leukoplakia				
Yes	612(7.08)	485(6.99)	127(7.48)	0.47
No	8028(92.92)	6475(93.01)	1571(92.52)	
Red and white lesions				0.52
Yes	680(7.87)	540(7.78)	140(8.24)	
No	7960(92.13)	6402(92.22)	1558(91.76)	
Candidiasis				<0.001
Yes	685(7.93)	508(7.32)	177(10.42)	
No	7955(92.07)	6434(92.68)	1521(89.58)	

Table 3. The associations between the oral lesions and diabetes mellitus in study participants using the crude and adjusted models (n = 8640)

Variable	Crude Model	*P*-Value	Adjusted Model	*P* Value
Diffuse oral pigmentation	0.57(0.49-0.67)	<0.001	0.82(0.7-0.97)	0.02
Non diffuse oral pigmentation	1.05(0.89-1.24)	0.55	1.02(0.85-1.22)	0.86
Oral exophytic lesions	1.10 (0.85-1.43)	0.449	0.81 (0.61-1.07)	0.133
Herpes	1.21(0.95-1.56)	0.115	1.01 (0.77-1.31)	0.96
Erythroplakia	1.09(0.62-1.89)	0.75	0.92(0.51-1.66)	0.77
Leukoplakia	1.07(0.87-1.31)	0.478	1.06(0.86-1.32)	0.57
Red and white lesions	1.06(0.87-1.29)	0.523	1.03(0.84-1.27)	0.76
Candidiasis	1.47(1.23-1.76)	<0.001	1.07(0.86-1.32)	0.55

The adjusted model is adjusted for confounding variables, including age (continuous variable), gender (male/female), education years (continuous variable), wealth status index (continuous variable), cigarette smoking (yes/no/former), opium use (yes/no), alcohol drinking (yes/no), body mass index (continuous variable), denture duration, and brushing (yes/no).

in the odds of developing leukoplakia (OR: 0.24; 95% CI: 0.06–1.00; $P = 0.05$). Conversely, no other statistically significant associations were found between various oral lesions and different treatment modalities among diabetic participants. Furthermore, the DM duration did not exhibit any significant correlations with the presence of oral lesions in this cohort of diabetic individuals.

Discussion

This cross-sectional study investigated the potential relationship between DM and the prevalence of oral lesions among participants in the RCS. The findings demonstrated that diabetic individuals had reduced odds of exhibiting diffuse oral pigmentation. Conversely, patients receiving insulin therapy showed increased odds of developing erythroplakia.

Numerous studies have consistently identified DM as a significant predisposing factor for various oral diseases, thus emphasizing the critical importance of routine oral health evaluations and ongoing surveillance in diabetic patients.[24-25] Furthermore, some researchers propose a direct correlation between specific oral manifestations and suboptimal metabolic control of DM.[25-26] Other researchers propose that the increased susceptibility to oral infections and changes within the oral cavity observed in diabetic patients may be attributed to immunological dysfunctions, such as impaired chemotaxis and phagocytosis, alongside microcirculatory complications that culminate in diminished blood flow.[27] In academic contexts, early insulin administration has been associated with a longer DM duration, suboptimal glycemic control, and an elevated susceptibility to chronic complications. These factors collectively contributed to detrimental effects on overall patient health and diminished quality of life.[28]

Systemic conditions that can cause oral pigmentation are thoroughly examined. Alterations in the color of the oral mucosa may result from the buildup of either endogenous or exogenous pigments, often due to various mucosal disorders.[29] The existence of oral pigmentation can be a crucial sign of an underlying systemic illness.[30] According to Mohsin et al's research, diabetic patients exhibit a higher incidence of oral mucosal changes when compared to non-diabetic individuals, with considerable differences in the progression and severity of these alterations between the two groups. The presence of a coated tongue, a cracked tongue, and benign conditions, such as migratory glossitis, varicose veins, melanin pigmentation, and leukoedema, were also identified as prevalent developmental oral mucosal findings in diabetic patients.[31] Melanocytes consistently present throughout the oral mucosa, yet they often go undetected due to their typically minimal pigment production. When these cells become activated, they possess the capacity to contribute to a range of conditions, encompassing both physiological pigmentation and various malignancies. Diagnosing oral pigmentations is often complex. A detailed examination may reveal underlying systemic conditions. Therefore, an exhaustive medical history and a comprehensive dermatological assessment are crucial initial steps. When a clinical diagnosis remains uncertain, a biopsy may be required to definitively exclude serious conditions, such as melanoma. Dermoscopy is a valuable diagnostic tool for distinguishing between various melanocytic lesions. However, despite its utility and the frequent inadequate examination of the oral cavity during dermatological assessments, there is limited published literature specifically addressing the dermoscopic evaluation of oral lesions. A systematic review classifies benign oral pigmented lesions into two main categories to aid in diagnosis and management: Diffuse lesions (e.g., physiological pigmentation, smoker's melanosis) and localized lesions (e.g., amalgam tattoos, melanocytic nevi).[32] In the present study, we observed lower odds of diffuse oral pigmentation in diabetic compared to non-diabetic patients, even after adjusting for confounding variables. Discrepancies in research findings may stem from multiple factors, encompassing differences in race, lifestyle behaviors, and definitions and measurements of oral pigmentation. Additionally, the type of study design

Table 4. The associations between the treatment type and diabetes mellitus duration and oral lesions among diabetic participants using the crude and adjusted models (n = 1698)

Variable			Crude Model	*P* Value	Adjusted Model	*P* Value
Diffuse	Treatment status	No treatment	1		1	
		Insulin therapy	0.99(0.53-1.85)	0.39	1.30(0.68-2.47)	0.42
		Pills	1.14(0.84-1.53)	0.97	1.31(0.95-1.80)	0.095
		Insulin therapy + pills	0.65(0.31-1.34)	0.24	0.74(0.35-1.56)	0.43
	Diabetes mellitus duration (continuous)		0.98(0.95-1.00)	0.05	0.99(0.97-1.02)	0.49
Non-diffuse	Treatment status	No treatment	1		1	
		Insulin therapy	0.96(0.51_1.81)	0.91	0.85(0.43-1.68)	0.8
		Pills	0.85(0.62-1.18)	0.34	0.92(0.66-1.28)	0.61
		Insulin therapy + pills	0.60(0.28-1.30)	0.20	0.08(0.37-1.76)	0.59
	Diabetes mellitus duration (continuous)		1.01(0.99-1.03)	0.23	1.01(0.98-1.03)	0.62
Oral exophytic lesions	Treatment status	No treatment	1	1	1	1
		Insulin therapy	1.11 (0.45-2.73)	0.94	0.86(0.33-2.19)	0.75
		Pills	0.78 (0.44-1.19)	0.20	0.72(0.43-1.20)	0.2
		Insulin therapy + pills	0.58(0.17-1.53)	0.31	0.35(0.08-1.53)	0.16
	Diabetes mellitus duration (continuous)		0.99(0.96-1.03)	0.76	0.97(0.93-1.01)	0.21
Herpes	Treatment status	No treatment	1	1	1	1
		Insulin therapy	1.55 (0.72-3.35)	0.40	1.34(0.61-2.97)	0.47
		Pills	0.77(0.48-1.24)	0.28	0.72(0.44-1.16)	0.18
		Insulin therapy + pills	0.70(0.24-2.03)	0.51	0.70(0.24-2.06)	0.52
	Diabetes mellitus duration (continuous)		1.00(0.97-1.03)	0.79	1.00(0.96-1.04)	0.97
Erythroplakia	Treatment status	No treatment	1	1	1	1
		Insulin therapy	5.66 (1.21-28.42)	0.035	6.80(1.23-37.45)	0.03
		Pills	1.72(0.45-6.54)	0.42	1.62(0.41-6.35)	0.36
		Insulin therapy + pills	4.00(0.66-24.29)	0.13	4.66(0.69-31.49)	0.11
	Diabetes mellitus duration (continuous)		1.02(0.95-1.09)	0.57	1.04(0.96-1.12)	0.37
Leukoplakia	Treatment status	No treatment	1	1	1	1
		Insulin therapy	0.23(0.05-0.99)	0.049	0.24(0.06-1.00)	0.05
		Pills	1.07(0.73-1.59)	0.70	1.09(074-1.63)	0.66
		Insulin therapy + pills	1.08 (0.49-2.37)	0.84	1.20(0.54-2.67)	0.66
	Diabetes mellitus duration (continuous)		0.59(0.28-1.22)	0.15	0.98(0.95-1.01)	0.45
Red and white lesions	Treatment status	No treatment	1	1	1	1
		Insulin therapy	0.58(0.22-1.49)	0.26	0.52(0.23-1.53)	0.28
		Pills	1.13(0.77-1.65)	0.51	1.14(0.78-1.68)	0.51
		Insulin therapy + pills	1.17(0.55-2.48)	0.67	1.3(0.61-2.80)	0.5
	Diabetes mellitus duration (continuous)		0.99(0.96-1.02)	0.55	0.99(0.96-1.02)	0.60
Candidiasis	Treatment status	No treatment	1	1	1	1
		Insulin therapy	1.03(0.54-1.93)	0.93	0.68(0.33-1.4)	0.3
		Pills	0.79(0.56-1.10)	0.17	0.73(0.50-1.06)	0.1
		Insulin therapy + pills	0.47(0.20-1.12)	0.09	0.50(0.19-1.27)	0.17
	Diabetes mellitus duration (continuous)		1.00(0.98-1.03)	0.67	1.00(0.97-1.02)	0.76

The adjusted model was adjusted for confounding variables, including age (continuous variable), gender (male/female), education years (continuous variable), wealth status index (continuous variable), cigarette smoking (yes/no/former), opium use (yes/no), alcohol drinking (yes/no), body mass index (continuous variable), denture duration, and brushing (yes/no).

and the analytical methods employed can contribute to variations in reported outcomes.

These intricate relationships underscore the necessity of considering numerous variables when interpreting the correlation between DM and oral pigmentation. Reduced salivary flow and compromised antimicrobial properties

of saliva can lead to infections. Furthermore, impaired immune responses and insufficient metabolic regulation significantly contribute to the development of infections.[33] Oral candidiasis is recognized as a common fungal infection.[34] Its prevalence is notably elevated in diabetic individuals, particularly those who use dentures, smoke, are on broad-spectrum antibiotics or steroids, and exhibit poor glycemic control.[35] While initial analyses suggested a higher incidence of oral candidiasis in diabetic patients, this association was no longer significant after controlling for these confounding variables. In a systematic review, L. Martorano-Fernandes et al determined that the prevalence of oral candidiasis in individuals with DM varied between 6.8% and 31%.[36] Similarly, a Sri Lankan study found Candida species in 81% of 250 diabetic individuals and in 81% of 81 non-diabetic individuals. However, the same study revealed that diabetic patients had significantly higher Candida counts (32.8%) compared to the non-diabetic control group (12.3%).[37] Another study revealed a higher proliferation of Candida colonies in oral samples from diabetic individuals with uncontrolled glucose levels (273.09 ± 54.15mg/dL) compared to those with controlled glucose levels (142.02 ± 31.17mg/dL) Interestingly, the number of Candida colonies in diabetic individuals was comparable to that found in non-diabetic individuals. A direct correlation was observed between the number of Candida colonies and salivary glucose concentration.[38]

The well-documented association between oral precancerous lesions (such as oral leukoplakia, erythroplakia, and OLP) and diabetic individuals is widely recognized in scientific literature.[35] A meta-analysis conducted by Gong et al further solidified this connection, demonstrating a significant correlation between an elevated risk of developing oral precancerous lesions and T2DM.[39] Parallel research conducted by Dikshit et al corroborated the link between DM and oral premalignant disorders.[40] Furthermore, Ramos-Garcia. highlighted that diabetic individuals faced an elevated risk of developing leukoplakia and erythroplakia.[41] A separate study conducted in Kerala demonstrated that diabetic patients were found to have double odds of developing leukoplakia and triple the odds of erythroplakia compared to their non-diabetic counterparts.[35] These findings are consistent with the observations of Ujpál et al who reported prevalence rates of 6% for leukoplakia and 2% for erythroplakia within diabetic populations.[42] Diabetic patients receiving insulin therapy were observed to have a greater likelihood of erythroplakia compared to their untreated counterparts in this study. This association may be attributable to insulin-like growth factor-I (IGF-I), a hormone with structural similarities to insulin, which has been implicated in the progression of oral premalignant lesions, including erythroplakia, in diabetic individuals.[43] However, a direct causal link between insulin therapy and erythroplakia pathogenesis has yet to be conclusively established.

de Souza Bastos et al identified leukoplakia in 2.7% of individuals with T2DM; however, this prevalence was not significantly different from that observed in control groups.[44] Conversely, a study conducted in India established a correlation between DM and the onset of leukoplakia, proposing that hyperglycemia may elevate the risk of malignancy across various oral leukoplakia subtypes.[45] Studies have indicated a higher prevalence of a certain condition in diabetic (6.2%) compared to non-diabetic individuals (2.2%), with the highest incidence observed in insulin-treated patients.[45] Furthermore, an analysis of Third National Health and Nutrition Examination Survey (NHANES III) data, which included 65 diabetic and 15,746 non-diabetic participants, corroborated a history of diabetes as an independent risk factor for leukoplakia[46.] In contrast to prior research that indicated a twofold increased risk of leukoplakia in diabetic compared to non-diabetic women,[40] the present study observed a marginally reduced likelihood of leukoplakia among diabetic individuals. This discrepancy may be attributable to differences in racial, cultural, socioeconomic, environmental, or age-related factors. Furthermore, the cross-sectional design of this study may contribute to these divergent findings, underscoring the need for further investigation through longitudinal follow-up studies.

A notable limitation of this study is its cross-sectional design, which inherently constrains the ability to establish causal relationships. Nevertheless, the research is strengthened by its population-based framework, a substantial sample size, and comprehensive documentation of both exposures (including cigarette and opium use) and confounding variables (including demographics, oral health status, and medical history).

Conclusion

This study concludes that diabetic patients exhibit a reduced likelihood of diffuse oral pigmentation. Additionally, individuals undergoing insulin therapy demonstrated an increased probability of erythroplakia. No association was observed between T2DM and other oral lesions. Future longitudinal research is advised to corroborate these relationships.

Acknowledgments

The authors would like to thank the study participants, the personnel at the study sites, and the members of Rafsanjan Cohort Center in Rafsanjan, Iran.

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Competing Interests
No conflict of interest.

Data Availability Statement
The datasets underpinning this study are not publicly accessible due to privacy constraints but are accessible from the corresponding author upon reasonable request.

Ethical Approval
This study's design adhered to the PERSIAN protocol and received approval from the Ethics Committee of Rafsanjan University of Medical Sciences (IR.RUMS.REC.1401.216). Furthermore, the research was conducted in accordance with the STROBE guidelines.

Funding
The authors confirm that the preparation of this manuscript did not involve any external funding, grants, or other forms of financial support.

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