Shiraz E-Med J. 2019 April; 20(4):e80081. doi: 10.5812/semj.80081.

Published online 2018 September 26. **Research Article**

Relationship Between Oral Presentations and Diabetic Micro-Vascular Complications

Akram Ghadiri-Anari [1], Nasim Namiranian [2], Narjes Hazar [3], Shadab Kharazmi [4], Maryam Jalili Sadrabad [5], Khatereh Kheirollahi [6,*], Azra Mohiti [6], Reyhane Azizi [7] and Mohsen Aliakbari [8]

[1] Associate Professor, Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Assistant Professor of Community and Preventive Medicine, Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Community Medicine Specialist. Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[4] MA General Psychology, Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[5] Assistant Professor, Department of Oral Medicine, Dental Faculty, Semnan University of Medical Sciences, Semnan, Iran
[6] Assistant Professor, Department of Oral Medicine, Dental Faculty, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[7] Assistant Professor, Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[8] Medical Student, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[*] *Corresponding author*: Assistant Professor, Oral Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Tel: +98-9135217174, E-mail: dds.kh.kheirollahi@gmail.com

Received 2018 June 02; **Revised** 2018 August 25; **Accepted** 2018 August 26.

Abstract

Background: Oral mucosal lesions are more prevalent in diabetic patients compared to healthy individuals. Periodontal disorders have been known as the sixth complication of diabetes mellitus after microvascular and cardiovascular complications. The aim of this research was to assess the relationship between oral mucosal lesions and retinopathy and nephropathy in type 2 diabetic subjects in the Yazd province.

Methods: This analytical cross-sectional study was conducted in diabetes research center during 2014 - 2016 in Yazd. Individuals with glomerular filtration rate (GFR) less than 60, oropharyngeal cancer, pregnancy, lactation, type one diabetes, or newly diagnosed diabetes (< 2 years) are excluded from study. The subjects' demographic data and oral examination was performed by an oral medicine specialist. Soft tissues oral cavity findings consist of any form of candidiasis, periodontitis, gingivitis, xerostomia, geographic tongue, lichen planus, gingival hyperplasia, delay oral wound healing, fissured tongue, and burning mouth sensation. Fasting blood sugar (FBS), HbA1c, and micro-albuminuria were checked. Diabetic nephropathy defined to the urinary excretion rate of albumin above 30 mg/g creatinine. The retinal specialist evaluated diabetic retinopathy. Finally, frequency of soft tissue oral lesions in individuals with and without retinopathy and nephropathy were compared. We analyzed data using the SPSS version 20. Statistical significance less than 0.05 were accepted.

Results: Totally, 274 patients (48% male) participated in this study. Most of the patients (70.8%) suffer from at least one of the diabetic microvascular complications (retinopathy, nephropathy or both) and 80 diabetic patients (29.2%) had no complications. Gingivitis (P = 0.049) and fissured tongue (P = 0.047) were more prevalent in retinopathic individuals compared to subjects without retinopathy. Fissured tongue and delayed wound healing were high in nephropathic persons compared to other groups (P = 0.047 and 0.039, respectively). Presence of at least one of the oral lesions are higher than in patients with retinopathy and nephropathy compared to individuals without complications (P = 0.047 and 0.049 respectively).

Conclusions: High frequency of oral problems in subjects with micro-vascular complications were found. Our findings showed that closer cooperation between the endocrinologist and the oral medicine specialist is required. In addition, diagnosis of oral problems in diabetics, especially with micro-vascular complications, is necessary to improve the oral health of them.

Keywords: Diabetes Mellitus, Retinopathy, Periodontitis, Nephropathy, Candidiasis

1. Background

Diabetes is a common metabolic disorder worldwide. Diabetes is one the major causes of death due to micro and macro-vascular complications (1, 2).

Various oral soft tissue presentations are associated with hyperglycemia. These complications include periodontitis and gingivitis, salivary gland dysfunction leading to low salivary flow rate and changes in salivary components, and disorders of taste. In addition, other oral problems consist of fungal and bacterial infections, geographic tongue, benign migratory glossitis, stomatitis, fissured tongue, lichen planus, lichenoid reaction, traumatic

ulcer, and angular chelitis (3-7).

In addition, high frequency of delayed mucosal wound healing, dental carries, and tooth loss has been reported in patients with diabetes compared to healthy individuals (8). The chance of initiation and progression of oral mucosal lesions were found to be high in diabetic patients compared to non-diabetic controls (9). Periodontal disorders have been known as the 6th complication of diabetes mellitus (10). Retinopathy and nephropathy are known micro-vascular complications of diabetes. Although relationships between oral mucosal lesions and diabetic retinopathy and nephropathy has not been fully explored. In one study, among normal weight subjects with type 2 diabetes, IgG titers for Porphyromonas gingivalis, an oral pathogen, were correlated with the urinary albumin excretion rate (11). The level of IL-6 in the vitreous fluid had positive correlation with the severity of periodontal disease in diabetic persons (12). Due to the lack of data in this field in our region, this study was set to assess the relationship between oral soft tissue presentations and nephropathy and retinopathy in type 2 diabetic subjects in the Yazd province with high prevalence of diabetes. Lotfi et al. in 2014, reported that 16.3% of people in the Yazd province (a city in the middle of Iran) suffered from known diabetes (13).

2. Methods

The study was an analytical cross-sectional, which was done in a diabetes research center during 2014 - 2016 in Yazd. Census sampling method was done. The inclusion criteria were type 2 diabetes mellitus (T2DM) on oral anti hyperglycemic agents or insulin therapy, patients older than 30 years, and at least 2 years known diabetes. If there were glomerular filtration rate (GFR) less than 60, oro-pharyngeal cancer, pregnancy, lactation, type one diabetes, or newly diagnosed diabetes (< 2 years) were excluded from the study. The subjects' demographic data and the data recorded in their files, consisting of age, gender, educational level, medications used, smoking or use of any other habit-forming drugs, use of toothbrushes, dental floss, and mouth rinses were recorded. All the subjects underwent history taking and thorough oro-dontal examination procedures. Oral examination was performed by an oral medicine specialist who had already been trained for the purpose of this study after evaluation of their files. The oral examinations were carried out under natural light by retracting the lips and cheeks in all the oral cavity areas. Oral lesions were diagnosed based on clinical views and biopsies were taken by the oral medicine specialist in suspected cases. In relation to the periodontal status, the definition presented in Carranza's clinical periodontology textbook (14) was used. The pathologic findings of the oral cavity soft tissues in the subjects consisted of candidiasis lesions, including different forms of oral candidiasis and related lesions, i.e. denture stomatitis, angular cheilitis, median rhomboid glossitis, and complete atrophy of lingual papilla. Non-candida lesions consisted of periodontitis, gingivitis, xerostomia, geographic tongue, lichen planus, gingival hyperplasia, delay oral wound healing, fissured tongue, and burning mouth sensation.

Fasting blood sugar (FBS), HbA1c, and microalbuminuria were checked in diabetes research center laboratory. Diabetic nephropathy defined to increase the excretion rate of urinary albumin above 30 mg/g creatinine (15), according to the last laboratory findings at least three months ago.

Evaluation of diabetic retinopathy was performed by an expert ophthalmologist (retinal specialist) during 6 months and available in the patient's medical file. The retinopathy grading was categorized as no retinopathy, mild none proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR). In our study, subjects were divided into two groups based up retinopathy examination, no retinopathy and the other group had a variable degree of retinopathy (mild, moderate, severe, and PDR). Finally frequency of soft tissue oral lesions in individuals with and without retinopathy and nephropathy were compared.

2.1. Research Ethics

This research was presented to the Ethics Committee of Shahid Sadoughi University of Medical Sciences and accepted by the Internal Medicine Department. The Ethics Committee approved the study with the number IR.SSU.REC.MEDICINE.REC.17/1/221184. The patients learned about the aim and study protocol, and written consent before the study was filled.

2.2. Statistical Analyses

The sample size was calculated based on the comparison of two proportions considering α: 0.05, β: 20%, and 10% differences. SPSS version 20.0 for Windows computer software package (SPSS Inc., Chicago, IL, USA) was applied. Studied population description was done by frequency (%), and mean (standard deviation). The normality of data were analyzed, Chi-square test (χ^2) and Fisher's exact test were done for analytic analysis. Binary logistic regression was done and odds ratios (ORs) were used to evaluate the risk factors associated with oral lesions in studied patients.

Statistical significance less than 0.05 were accepted.

3. Results

During the study period, 1509 diabetic patients were examined, totally, 274 patients (48% male) fulfilled the inclusion criteria without exclusion. Most of the patients (70.8%) suffer from at least one of the diabetic microvascular complications (retinopathy, nephropathy or both) and 80 diabetic patients (29.2%) had no microvascular complications. Descriptive characteristics of patients were shown in Table 1.

Tables 2 and 3 show the oral lesion frequency among patients with and without microvascular complications and oral lesions are more prevalent in patients with retinopathy (P = 0.047) and nephropathy (P = 0.049).

The binary logistic regressions showed that age, duration of diabetes, and HbA1c were not statistically associated with oral lesion frequency in type 2 diabetic patients (Table 4).

4. Discussion

Periodontal problems have been known as the sixth complication after microvascular and cardiovascular complications of diabetes mellitus (10). Probable mechanisms of periodontal disease maybe differences in the subgingival microflora (16), dysfunction of immune cells, high level of tumor necrosis factor-α (17), advanced glycation end products (18), and increase in messenger RNA for RAGEs (receptors for AGEs) in the periodontal organs of type 2 diabetics compared to healthy subjects (19). This study was designed to compare the frequency of oral soft tissue lesions between diabetics with microvascular involvement (retinopathy and nephropathy) and without involvement.

In this article, base line characteristics of subjects with and without micro-vascular complications such as age and duration of diabetes differ. Due to the fact that microvascular complications happen with advancing and prolongation of disease, age and duration of diabetes of individuals with micro-vascular complications is higher than the other group. Smoking is associated with periodontal disease (20, 21) and may confound the results, however, smoking in subjects with and without micro-vascular complications did not differ.

Gingivitis and fissured tongues were more prevalent in retinopathic persons compared to other groups. Frequency of other soft tissue lesions was not different with respect to retinopathy.

Song et al. showed that diabetic retinopathy had positive correlation with periodontitis in normal weight diabetic Korean adults (22). Other oral lesions were not evaluated in this study. In addition, sample size was greater than our study. Another study revealed positive correlation between the level of IL-6 in the vitreous fluid and severity of periodontal disease in diabetes (12). In the mentioned studies, both gingivitis and periodontitis categorized as periodontitis but these lesions categorized separately in our research. Gingivitis is mild degree of periodontitis that is statistically significant differences between retinopathy and other group in our study. In addition, retinopathy was significantly higher among diabetics with oral diseases in Bajaj et al. study (23). Association between median rhomboid glossitis (a form of candidiasis) and retinopathy was seen in Guggenheimer et al. study (7). This association was not seen in our study, although median rhomboid glossitis categorized as a sub-group of candidiasis in our article.

Fissured tongue in diabetic persons was higher than healthy non diabetic subjects (24), however, correlation of this lesion with retinopathy was not assessed in the mentioned article. In our study, fissured tongue was more prevalent in retinopathic persons than other groups. Future studies maybe helpful in this regard.

In addition, we compared the frequency of the presence of at least one of the oral lesions in retinopathy and normal group. Results showed a statistically significant difference between two groups. Due to the fact that some baseline characteristics of two groups differs, it may be possible that confounding factors such as age, duration of T2DM, and HbA1c affect these results. Therefore, the regression model was used. This test showed that the change in age, duration of diabetes, and HbA1c do not influence the oral lesion frequency in type 2 diabetic patients.

Fissured tongue and delayed wound healing were more prevalent in nephropathic persons compared to other groups. Frequency of other soft tissue lesions was not differing with respect to nephropathy. Association between median rhomboid glossitis (a form of candidiasis) and neohropathy was seen in the study of Guggenheimer et al. (7).

One longitudinal study of diabetes and complications showed that periodontitis predicts development of overt nephropathy in type 2 diabetic subjects (25).

In one study, IgG titers for Porphyromonas gingivalis, were positive correlations with the urinary albumin excretion ratio among non-obese subjects with type 2 diabetes (11).

Naruishi et al. showed higher rate of periodontal problems in patients with diabetic nephropathy and negative correlation between glomerular filtration rate and the number of missing teeth in Japanese adults (26). Missing teeth were not evaluated in our study. In addition, we exclude subjects with glomerular filtration rate (GFR) less than 60 in the study; therefore, it is not possible to assess this variable. In the study of Bajaj, association was not seen

Table 1. Descriptive Characteristics of Studied Patients

Variables	Micro-Vascular Complications		P Value
	Yes	No	
Age, y (mean ± SD)	59.47 ± 9.5	54.75 ± 11.11	0.001
Gender, male (%)	87 (52.7)	45 (35)	0.063
Smoker (%)	13 (7.9)	8 (7.1)	0.889
Duration of diabetes (mean ± SD)	10.48 ± 5.41	6.30 ± 5.12	0.001
FBS, mg/dL (mean ± SD)	154.57 ± 45.43	146.67 ± 41.63	0.158
HbA1c% (mean ± SD)	8.01 ± 1.33	7.56 ± 1.28	0.071

Table 2. Oral Lesion Frequency Comparison in Patients with and Without Retinopathy

Oral Lesions	Retinopathy		P Value
	Yes (N = 130)[a]	No (N = 143)[a]	
Candidiasis	29 (22.3)	38 (26.6)	0.402
Gingivitis	19 (14.7)	12 (8.55)	0.049
Xerostomia	39 (30)	42 (29.4)	0.500
Geographic tongue	22 (16.9)	16 (11.2)	0.065
Gingival hyperplasia	6 (4.6)	4 (2.8)	0.317
Fissured tongue	12 (9.2)	6 (4.2)	0.047
Burning mouth sensation	12 (9.2)	9 (6.3)	0.247
Lichen planus	5 (3.8)	7 (4.9)	0.397
Periodontitis	50 (38.5)	63 (44.1)	0.303
Delayed wound healing	14 (10.8)	11 (7.7)	0.435
Presence of at least one of the oral lesions	120 (91.2)	69 (48.2)	0.047

[a]Values are expressed as No. (%).

Table 3. Oral Lesion Frequency Comparison in Patients with and Without Nephropathy

Oral Lesions	Nephropathy		P Value
	Yes (N = 118)[a]	No (N = 156)[a]	
Candidiasis	31 (26.5)	36 (23.1)	0.424
Gingivitis	11 (9.5)	20 (12.9)	0.51
Xerostomia	27 (23.1)	54 (34.6)	0.053
Geographic tongue	18 (15.4)	20 (12.8)	0.332
Gingival hyperplasia	5 (4.3)	5 (3.2)	0.439
Fissured tongue	8 (6.8)	10 (6.4)	0.047
Burning mouth sensation	7 (6)	14 (9)	0.248
Lichen planus	2 (1.7)	4 (2.6)	0. 31
Periodontitis	46 (39.3)	67 (42.9)	0.67
Delayed wound healing	16 (13.7)	9 (5.8)	0.039
Presence of at least one of the oral lesions	105 (88.9)	85 (54.2)	0.049

[a]Values are expressed as No. (%).

between nephropathy and oral presentations of diabetes (23).

Although fissured tongue was higher in diabetic persons compared to healthy non-diabetic subjects (24), correlation of this lesion with nephropathy was not assessed in the mentioned article. In our study, fissured tongue was more prevalent in subjects with nephropathy than other groups. Future studies may be helpful in this regard.

Vesterinen et al. evaluated oral presentation of individuals with diabetic nephropathy and other cause of nephropathy in persons with chronic kidney disease (CKD). Results showed increased dental caries in subjects

Table 4. The Binary Logistic Regression Odds Ratios (and 95% CIs) for Risk Factors Associated with Oral Lesion in Type 2 Diabetes

Factors	Odds Ratio (95% CI)	P Value
Age, y	0.975 (0.706 - 1.19)	0.302
Duration of diabetes, y	1.053 (0.484 - 1.76)	0.298
HbA1c%	1.404 (0.982 - 1.47)	0.145

with diabetic nephropathy than other cause of nephropathy. In addition, lower stimulated salivary flow rate in diabetic patients than other CKD individuals was seen. Periodontal health of two groups did not differ (27).

Etiology of delayed oral wound healing in diabetes include decreased vascularization, low blood flow, dysfunction of innate immunity, decreased production of growth factor, and emotional stress (28).

Delay mucosal wound healing has been reported in patients with diabetes (8). No article was found in the high rate of delayed oral wound healing in the diabetic nephropathy persons. Although, it is possible that with the duration of diabetes and initiation of micro-vascular complications, other unusual presentation happens.

Finally, we compare frequency of presence of at least one of the oral lesions in nephropathy and normal groups. Results showed statistically significant difference between two groups. Due to some baseline differences of two groups, the regression model was used. This test showed that the change in age, duration of diabetes, and HbA1c do not influence on the oral lesion frequency in type 2 diabetic patients.

This article had some limitations such as study design (cross-sectional), therefore, it is not possible to determine a causality relationship. In addition, with regard to high prevalence of diabetes and two years sampling period in this study, the limited sample size remain as a major limitation of this study. Future studies with large sample size may be necessary. It is noticeable that for evaluation causality of diabetes microvascular complication on oral lesions, some studies with large sample size and prospective design are needed. Finally, we did not assess other comorbidities such as hypertension and obesity, which may be as the confounders.

4.1. Conclusion

High frequency of oral presentations in subjects with micro-vascular complications compared to other groups were found. Closer cooperation between oral medicine specialist and endocrinologist is required and effective in managing diabetic patients. Knowledge of oral problems among people with diabetes, especially with microvascular complications, is necessary to improve the oral health of diabetic patients.

Acknowledgments

We sincerely thank the patients that participated in this study as well as the personnel of the diabetes research center in Yazd, Iran who were involved in collecting and processing the data.

Footnotes

Conflicts of Interests: There are no conflict of interests.

Funding/Support: This study was conducted with a financial support that was provided by Shahid Sadoughi University of Medical Sciences.

References

1. Moore PA, Zgibor JC, Dasanayake AP. Diabetes: A growing epidemic of all ages. *J Am Dent Assoc*. 2003;**134 Spec No**:11S–5S. [PubMed: 18196668].
2. Jain S, Saraf S. Type 2 diabetes mellitus-Its global prevalence and therapeutic strategies. *Diabetes Metab Syndr Clin Res Rev*. 2010;**4**(1):48–56. doi: 10.1016/j.dsx.2008.04.011.
3. Sandberg GE, Sundberg HE, Fjellstrom CA, Wikblad KF. Type 2 diabetes and oral health: A comparison between diabetic and non-diabetic subjects. *Diabetes Res Clin Pract*. 2000;**50**(1):27–34. [PubMed: 10936666].
4. Chomkhakhai U, Thanakun S, Khovidhunkit SP, Khovidhunkit W, Thaweboon S. Oral health in Thai patients with metabolic syndrome. *Diabetes Metab Syndr Clin Res Rev*. 2009;**3**(4):192–7. doi: 10.1016/j.dsx.2009.08.004.
5. Collin HL, Niskanen L, Uusitupa M, Toyry J, Collin P, Koivisto AM, et al. Oral symptoms and signs in elderly patients with type 2 diabetes mellitus. A focus on diabetic neuropathy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;**90**(3):299–305. [PubMed: 10982950].
6. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, et al. Insulin-dependent diabetes mellitus and oral soft tissue pathologies. I. Prevalence and characteristics of non-candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;**89**(5):563–9. [PubMed: 10807712].
7. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, et al. Insulin-dependent diabetes mellitus and oral soft tissue pathologies: II. Prevalence and characteristics of Candida and Candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;**89**(5):570–6. [PubMed: 10807713].
8. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. *J Am Dent Assoc*. 2008;**139 Suppl**:19S–24S. [PubMed: 18809650].
9. Saini R, Al-Maweri SA, Saini D, Ismail NM, Ismail AR. Oral mucosal lesions in non oral habit diabetic patients and association of diabetes mellitus with oral precancerous lesions. *Diabetes Res Clin Pract*. 2010;**89**(3):320–6. doi: 10.1016/j.diabres.2010.04.016. [PubMed: 20488573].
10. Loe H. Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care*. 1993;**16**(1):329–34. [PubMed: 8422804].
11. Kuroe A, Taniguchi A, Sekiguchi A, Ogura M, Murayama Y, Nishimura F, et al. Prevalence of periodontal bacterial infection in non-obese Japanese type 2 diabetic patients: Relationship with C-reactive protein and albuminuria. *Horm Metab Res*. 2004;**36**(2):116–8. doi: 10.1055/s-2004-814221. [PubMed: 15002063].

12. Noma H, Sakamoto I, Mochizuki H, Tsukamoto H, Minamoto A, Funatsu H, et al. Relationship between periodontal disease and diabetic retinopathy. *Diabetes Care*. 2004;**27**(2):615. [PubMed: 14747249].
13. Lotfi MH, Saadati H, Afzali M. Prevalence of diabetes in people aged >/= 30 years: The results of screen-ing program of Yazd province, Iran, in 2012. *J Res Health Sci*. 2014;**14**(1):87–91. [PubMed: 24402857].
14. Newman MG, Takei H, Klokkevold PR, Carranza FA. *Carranza's clinical periodontology*. Elsevier health sciences; 2014.
15. Toto RD. Microalbuminuria: Definition, detection, and clinical significance. *J Clin Hypertens (Greenwich)*. 2004;**6**(11 Suppl 3):2–7. [PubMed: 15538104].
16. American Academy of Periodontology. Parameter on periodontitis associated with systemic conditions. *J Periodontol*. 2000;**71**(5 Suppl):876–9. doi: 10.1902/jop.2000.71.5-S.876. [PubMed: 10875698].
17. Naguib G, Al-Mashat H, Desta T, Graves DT. Diabetes prolongs the inflammatory response to a bacterial stimulus through cytokine dysregulation. *J Invest Dermatol*. 2004;**123**(1):87–92. doi: 10.1111/j.0022-202X.2004.22711.x. [PubMed: 15191547].
18. Wang J. Glucose biosensors: 40 years of advances and challenges. *Electroanalysis*. 2001;**13**(12):983–8. doi: 10.1002/1521-4109(200108)13:12<983::aid-elan983>3.0.co;2-#.
19. Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. *Diabetes Care*. 2005;**28**(3):555–9. [PubMed: 15735187].
20. Kinane DF, Chestnutt IG. Smoking and periodontal disease. *Crit Rev Oral Biol Med*. 2000;**11**(3):356–65. [PubMed: 11021635].
21. Heasman L, Stacey F, Preshaw PM, McCracken GI, Hepburn S, Heasman PA. The effect of smoking on periodontal treatment response: A review of clinical evidence. *J Clin Periodontol*. 2006;**33**(4):241–53. doi: 10.1111/j.1600-051X.2006.00902.x. [PubMed: 16553633].
22. Song SJ, Lee SS, Han K, Park JB. Periodontitis is associated with diabetic retinopathy in non-obese adults. *Endocrine*. 2017;**56**(1):82–9. doi: 10.1007/s12020-016-1215-z. [PubMed: 28032209].
23. Bajaj S, Prasad S, Gupta A, Singh VB. Oral manifestations in type-2 diabetes and related complications. *Indian J Endocrinol Metab*. 2012;**16**(5):777–9. doi: 10.4103/2230-8210.100673. [PubMed: 23087863]. [PubMed Central: PMC3475903].
24. Bastos AS, Leite AR, Spin-Neto R, Nassar PO, Massucato EM, Orrico SR. Diabetes mellitus and oral mucosa alterations: Prevalence and risk factors. *Diabetes Res Clin Pract*. 2011;**92**(1):100–5. doi: 10.1016/j.diabres.2011.01.011. [PubMed: 21300417].
25. Shultis WA, Weil EJ, Looker HC, Curtis JM, Shlossman M, Genco RJ, et al. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. *Diabetes Care*. 2007;**30**(2):306–11. doi: 10.2337/dc06-1184. [PubMed: 17259499].
26. Naruishi K, Oishi K, Inagaki Y, Horibe M, Bando M, Ninomiya M, et al. Association between periodontal condition and kidney dysfunction in Japanese adults: A cross-sectional study. *Clin Exp Dent Res*. 2016;**2**(3):200–7. doi: 10.1002/cre2.39. [PubMed: 29744168]. [PubMed Central: PMC5839219].
27. Vesterinen M, Ruokonen H, Furuholm J, Honkanen E, Meurman JH. Oral health in predialysis patients with emphasis on diabetic nephropathy. *Clin Oral Investig*. 2011;**15**(1):99–104. doi: 10.1007/s00784-009-0360-7. [PubMed: 20084416].
28. Abiko Y, Selimovic D. The mechanism of protracted wound healing on oral mucosa in diabetes. Review. *Bosn J Basic Med Sci*. 2010;**10**(3):186–91. doi: 10.17305/bjbms.2010.2683. [PubMed: 20846123]. [PubMed Central: PMC5504493].