

The relationship between periapical lesions and the serum levels of glycosylated hemoglobin and C-reactive protein in type 2 diabetic patients

Mohammad S. Al-Zahrani, BDS, PhD, Basel M. Abozor, BDS, MSc, Khalid H. Zawawi, BDS, DSc.

ABSTRACT

الأهداف: دراسة العلاقة بين الآفات الذروية ومستويات الهيموجلوبين السكري (HbA1c) وبروتين سي إرتكاسي (CRP) في الدم لدى مرضى النوع الثاني من داء السكري.

الطريقة: أجريت هذه الدراسة المقطعية في كلية ابن سينا الأهلية للعلوم الطبية، جدة، المملكة العربية السعودية، خلال الفترة من سبتمبر 2013م إلى فبراير 2015م. تم الحصول على معلومات التاريخ المرضي والبيانات الاجتماعية الديمغرافية من المشاركين، كما تم فحص حالة الأسنان واللثة وتم الحصول على عينات من الدم لتحديد نسبة HbA1c و مستويات CRP. كما تم تسجيل وجود الآفات الذروية من صور الأشعات السينية، ومن ثم تم تحليل النتائج إحصائياً.

النتائج: شملت الدراسة 100 من مرضى داء السكري -النوع الثاني، وقد كان متوسط عمر المشاركين 48.9 ± 8.5 سنة. كما كانت نسبة المشاركين الذين لا يوجد لديهم آفات ذروية 14% في حين وُجد أن 25% من العينة لديهم 1 أو 2 من الآفات، و32% لديهم 3 أو 4 آفات، بينما 29% من العينة كان لديهم 5 أو أكثر من الآفات الذروية. وكانت نسبة الهيموجلوبين السكري $9.8\% (\pm 2.5)$ و بروتين سي إرتكاسي $6.9 (\pm 6.3)$ ملغم/لتر. كما أشارت النتائج أن وجود الآفات الذروية لها علاقة إحصائية مع ارتفاع مستوى الهيموجلوبين السكري في الدم وأيضاً مع بروتين سي إرتكاسي.

الخلاصة: أظهرت الدراسة أن وجود الآفات الذروية لها علاقة بارتفاع الهيموجلوبين السكري وبروتين سي إرتكاسي في الدم لدى مرضى داء السكري - النوع الثاني.

Objectives: To investigate the relationship between the presence of periapical lesions (PL) and levels of glycosylated hemoglobin (HbA1c), and C-reactive protein (CRP) in patients with type 2 diabetes.

Methods: This cross-sectional study was conducted at Ibn Sina National College for Medical Studies, Jeddah, Kingdom of Saudi Arabia, between September 2013 and February 2015. Medical and dental history and Sociodemographic data were obtained from participants. Dental and periodontal examinations were conducted and blood samples were obtained to determine levels

of HbA1c and CRP. The presence of PL was recorded from panoramic and periapical radiographs. Descriptive statistics and multivariable linear and logistic regression models were used for data analyses.

Results: One hundred patients were included; mean age was 48.9 ± 8.5 years. Of these patients, 14% had no PL, whereas 25% had one or 2 lesions, 32% had 3 or 4 lesions, and 29% had ≥ 5 PL. The mean HbA1c was $9.8\% (\pm 2.5)$ mg/L and CRP was 6.9 mg/L (± 6.3). The presence of PL was significantly associated with a higher level of HbA1c independent of age, gender, probing depth, and plaque index ($p=0.023$). Individuals with PL were also more likely to have a high CRP level (>3 mg/L) independent of the previous covariates (odds ratio: 1.19; 95% confidence interval: 1.01-1.41).

Conclusion: Periapical lesions are associated with a poorer glycemic control and a higher CRP level in type 2 diabetic patients.

Saudi Med J 2017; Vol. 37 (1): 36-40
doi: 10.15537/smj.2017.1.16052

From the Departments of Periodontics (Al-Zahrani), Orthodontics (Zawawi), Faculty of Dentistry, King Abdulaziz University, and the Department of Endodontics (Abozor), Ibn Sina National College for Medical Studies, Jeddah, Kingdom of Saudi Arabia.

Received 8th August 2016. Accepted 26th October 2016.

Address correspondence and reprint request to: Dr. Basel M. Abozor, Department of Endodontics, Ibn Sina National College for Medical Studies, Jeddah, Kingdom of Saudi Arabia. E-mail: drbasel1@yahoo.com
ORCID: <http://orcid.org/0000-0002-5511-4238>

Disclosure. Authors have no conflict of interest, and the work was not supported or funded by any drug company. This study was funded by the Deanship of Scientific Research, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia (Grant No. 165-216-D1435).

Type 2 diabetes is a complex multifactorial disease that results from insulin resistance and relative insulin deficiency.¹ Type 2 diabetes affects the immune system and is coupled with compromised immune response that leads to chronic inflammation, gradual tissue breakdown, and reduced ability for tissue repair.² Diabetes is becoming a major health concern as the prevalence of type 2 diabetes continues to increase worldwide and is considered by some as a new epidemic. In Saudi Arabia, for example, a recent systematic review reported a prevalence of 32.8% and the predicted prevalence of 35.4% in 2020 and reaching 45.4% in 2030.³ Oral symptoms of uncontrolled diabetes may comprise a plethora of conditions, such as dry mouth, tooth decay, periodontal diseases, delayed wound healing, and increased incidence of infection following surgery.⁴ The probable relationship between chronic oral infections, such as chronic apical periodontitis and periodontal diseases, and systemic health is an intriguing facet confronted by the medical and dental profession.^{5,6} The prevalence of periapical infection is estimated to be between 0.6-13.3%.⁷ Periapical infection is caused by microbiotas similar to those that cause periodontal disease.⁵ A bidirectional relationship between periodontal disease and diabetes has been extensively studied.^{8,9} A consistent relationship between diabetes and an increased risk of periodontitis has been shown and the magnitude of this increased risk is dependent on the level of glycosylated hemoglobin (HbA1c). Periodontal infection was also found to compromise diabetic status and its treatment was shown to improve glycemic control.⁸ The research on the pathogenesis, progression, and healing of periapical infections in diabetic patients is relatively limited.^{5,10} For example, in an animal study, hyperglycemia was found to negatively effect the pulpal healing in rats.¹¹ A more recent animal study showed that the presence of periapical and periodontal infections adversely influences the glycemic condition of diabetic rats and increased the HbA1c levels in normoglycemic rats.¹² Segura-Egea et al¹³ in a retrospective cohort study, found that the prevalence of apical periodontitis in diabetic patients to be more compared with controls (81.3% versus 58%). An epidemiological study of native Americans conducted to identify factors influencing the retention of endodontically treated teeth showed that diabetes was one of the factors associated with a decreased retention of root-filled teeth.¹⁴ A recent cross-sectional study found that periapical lesions were more common in diabetics than in non-diabetic controls.¹⁵ Schulze et al¹⁶ proposed the potential influence of periapical infection on diabetes control in a case of

type-1 diabetic patient. An increase in insulin demand was noticed prior to endodontic intervention, which was significantly decreased one day following root canal preparation.

The C-reactive protein (CRP) is an acute phase pentameric protein that is found in blood plasma and secreted by the liver, and its level rises in response to inflammation. CRP expression is regulated principally by interleukin-6. The primary biological function of CRP is recruiting the complement system and macrophages to mediate the elimination of pathogens and the host necrotic cells.¹⁷ It has been shown that hyperglycemia stimulate the secretion of interleukin-6 and tumor necrosis factor-alpha which leads to the increased secretion of serum CRP.¹⁸ Conversely, it has been reported that CRP could increase the risk of diabetes.¹⁹ Inflammation is most frequently caused by infection or tissue injury. C-reactive protein is the commonly used inflammatory biomarker and its importance and clinical usefulness has been reported extensively.²⁰ Periapical lesions are predominantly chronic diseases of infectious origin that cause chronic inflammatory reactions and it was shown that CRP is significantly increased in apical inflammation.²¹ Since HbA1c is the standard test for monitoring diabetes and CRP is an important marker for subclinical systemic inflammation, this study was aimed to investigate if there is a relationship between the presence of periapical lesions and serum levels of HbA1c and CRP in type 2 diabetic patients.

Methods. This cross-sectional study was conducted at Ibn Sina National College for Medical Studies in Jeddah, Kingdom of Saudi Arabia, between September 2013 and February 2015. Patients who were seeking dental treatment who satisfied the inclusion/exclusion criteria were asked to participate in the study. The inclusion criteria were: patients older than 30 years, history of type 2 diabetes mellitus (DM) for more than 5 years diagnosed according to the American Diabetes Association,⁴ absence of cognitive impairment, and agreed to undergo clinical and radiographic examination, and the required laboratory tests. Exclusion criteria included: type 1 diabetics and immune compromised patients, patient on antibiotic treatment or those who had received such treatment in the previous 3 months, smoking, pregnant women, and patients with less than 20 remaining teeth or presented with acute periodontal or periapical conditions. The research was conducted in accordance with the principles of the Helsinki Declaration and the study was reviewed and approved by the ethics committee of Ibn Sina National College

for Medical Studies, and an informed consent was obtained from participants prior to their enrollment. Age, gender, level of education, and medical and dental history were obtained from each participant. Panoramic and periapical radiographs were taken and a calibrated examiner recorded the number of teeth with periapical lesion. The periapical status was judged using the periapical index method proposed by Orstavik et al.^{22, 23} When a score of 3 or more was given, the tooth was considered as having a periapical lesion. For multirooted teeth, the root with the highest periapical index score was recorded. The periapical index scores were recorded for root-filled or non-filled teeth. Prior to starting the study, the examiner was calibrated and intra-examiner reliability for periapical index scores was evaluated by rescoring radiographs of 20 patients not involved in the study and the Cohen's kappa value was 0.93.

Periodontal assessments consisted of the following: probing depth (PD), bleeding on probing (BOP), plaque index (PI), and the number of teeth present was completed by a calibrated examiner. Intra-examiner reliability was assessed in 10 subjects not involved in the study and the reliability was 90% for recording the probing depth within 1mm. An experienced phlebotomist obtained the blood sample from each participant at Ibn Sina National College hematology laboratory to determine the levels of serum glycosylated hemoglobin (HbA1c) and C-reactive protein (CRP). Clinical and radiographic examinations and collection of blood samples was carried out on the same day for each participant.

Statistical analysis. The results are presented as mean \pm standard deviation (SD). Comparisons between males and females for the studied variables were performed using an independent sample t-test. Linear regression model was used to test the association between HbA1c and different variables, whereas logistic regression model

was used for the CRP and different variables. A value of $p < 0.05$ was considered to be significant. Statistical analyses were performed using the Statistical Package for Social Sciences (IBM Corp., Armonk, NY, USA) version 20.

Results. The first 100 patients who satisfied the inclusion/exclusion criteria were included. Of these, 14% had no periapical lesions, whereas 25% had one or 2 lesions, 32% had 3 or 4 lesions, and 29% had 5 or more periapical lesions. The characteristics and periodontal status of diabetic type 2 patients and their HbA1c and CRP levels are presented in Table 1. The mean age for the study sample was 49.0 ± 8.5 years. The sample comprised of 60 males and 40 females with no statistical significant difference in age ($p=0.07$). Also, Table 1 shows that there were no significant differences between males and females in HbA1c and CRP levels, and number of teeth and periodontal parameters. In the multivariable linear regression model, as shown in Table 2, the presence of periapical lesions was significantly associated with a higher level of HbA1c independent of age, gender, probing depth, and plaque index ($p=0.023$). Table 3 shows that individuals with periapical lesions were also more likely to have a high CRP level (>3 mg/L) independent of the previous covariates (odd ratio: 1.19; 95% confidence interval: 1.01-1.41). Furthermore, independent sample t-test showed that subjects with HbA1c values of $\geq 9\%$ had significantly more number of periapical lesions (mean= 3.8 ± 3.3) compared with those with $<9\%$ HbA1c levels (mean= 2.6 ± 2.2), ($p=0.047$). A trend was also seen for CRP levels where subject with CRP values of >3 mg/L had more number of periapical lesions (mean= 3.7 ± 3.2) compared with those with ≤ 3 mg/L CRP levels (mean= 2.7 ± 2.6) but it was not statistically significant, $p=0.07$.

Table 1 - Characteristic of the study sample and comparison between males and females.

Variables	Males	Females	Total	P-value
N of patients	60	40	100	-
N of patients with PL	49	37	86	0.13
Age (years)	50.1 ± 7.5	46.9 ± 9.6	49.0 ± 8.5	0.07
Number of teeth	24.1 ± 4.0	23.8 ± 3.9	24.0 ± 3.9	0.7
Number of PL	3.9 ± 3.5	3.3 ± 2.2	3.79 ± 3.1	0.3
HbA1c (%)	10.1 ± 2.6	9.5 ± 2.4	9.8 ± 2.5	0.3
CRP (mg/L)	6.6 ± 6.9	7.4 ± 5.4	6.9 ± 6.3	0.5
Probing depth (mm)	2.9 ± 0.8	2.7 ± 0.6	2.8 ± 0.8	0.1
Bleeding score (%)	60.4 ± 26.7	61.7 ± 24.7	60.9 ± 25.8	0.8
Plaque score (%)	40.7 ± 36.4	54.6 ± 37.8	46.2 ± 37.4	0.7

Data are presented as mean \pm standard deviation except number of patients and number of patients with periapical lesions (PL) that are presented as numbers. HbA1c - glycosylated hemoglobin, CRP - C-reactive protein, N - number

Table 2 - Predictors of glycosylated hemoglobin in the linear regression models.

Variable	Unstandardized coefficients		Standardized coefficients	t-test	P-value
	B-coefficient	Standard error	Beta		
Age	0.012	0.027	0.040	0.444	0.658
Males	0.061	0.476	0.012	0.128	0.899
Plaque score	-0.004	0.006	-0.064	-0.689	0.493
Probing depth	1.379	0.299	0.422	4.617	0.001*
Number of periapical lesions	0.176	0.076	0.210	2.307	0.023*

* Significant difference

Table 3 - Predictors of high levels of C-reactive protein (>3 mg/L) in the logistic regression models.

Variable	B-coefficient	Standard error	Odds ratio	95% Confidence interval		P-value
Age	-0.038	0.027	0.962	0.913	1.014	0.150
Males	1.120	0.490	3.065	1.174	8.001	0.022*
Probing depth	0.481	0.316	1.618	0.871	3.005	0.128
Plaque score	-0.008	0.006	0.992	0.979	1.004	0.190
Number of periapical lesions	0.173	0.088	1.189	1.001	1.412	0.049*

* Significant difference

Discussion. This cross-sectional study investigated the relationships between periapical lesions and the serum levels of HbA1c and CRP in type 2 diabetic patients. The results revealed that a significant relation does exist. The presence of periapical lesions was significantly related to higher levels of both HbA1c and CRP. Furthermore, periapical lesions were more frequent in uncontrolled type 2 diabetics. The results of the current study support a previous finding, which showed that periapical lesions were more prevalent in type 2 diabetics when compared with non-diabetics.¹⁵ The present results also are in line with the results of the study by Mesgarani et al,²⁴ where they found a higher frequency of periapical lesions in long-term diabetes when compared with short-term diabetes. The data on the relationship between periapical lesions and systemic CRP levels in type 2 diabetic patients could not be validated nor compared with other studies due to lack of previous reports.

Diabetic patients have increased susceptibility to chronic infection and inflammation of the oral tissues, especially when they are poorly controlled. Infection on the other hand can compromise diabetic status and results in high HbA1c level, which could explain the relationship between HbA1c and presence of periapical lesions in the present study. While the observed increase in the CRP level in the presence of periapical lesions could be due to an increase in the infection burden. C-reactive protein is an acute phase protein that is significantly increased in the presence of infection and

inflammation. Inflammation of the periapical area is mainly a consequence to bacterial infection of the tooth pulp.¹⁰ Periapical infection causes several local tissue responses to limit the spread of the infection. This infection leads to activation of the innate immunity. Gram-negative bacteria produce lipopolysaccharide that causes periapical inflammation through the initiation of intracellular pathways on inflammatory cells and up-regulation of proinflammatory cytokines, for example IL-1beta, IL-8, TNF-alpha, and prostaglandin E2. These cytokines could pass into the systemic circulation and then interact with free fatty acids, as well as advanced glycated end-products, that is characteristic of type 2 diabetes.^{10,25-28} The activation of this inflammatory cascade could stimulate an increase in insulin resistance and cause modification in the metabolic mechanism of type 2 diabetics. Hyperglycemia impairs collateral circulation and subsequently produces diverse changes in pulp and periapical tissues.²⁹ The increase in glucose levels may inhibit the function of macrophages, initiating an inflammatory condition that impairs cellular proliferation of the host resulting in delayed wound healing of the pulp and periapical tissues.¹¹ Additionally, the inflammatory response in the presence of hyperglycemia can be associated with a decrease in osteoprotegerin and IL-4,³⁰ and an up-regulation in certain cytokines.^{29,31}

One limitation for this study is being cross-sectional and henceforth, a cause and effect relationship cannot be concluded. Another limitation is that the recruited

sample was taken from a group of patients at one institution; thus, the findings cannot be generalized.

In conclusion, the results of this study showed that the number of periapical lesions was significantly associated with a higher serum level of HbA1c. Uncontrolled type 2 diabetics had higher number of periapical lesions. The presence of periapical lesions was also significantly associated with a high serum level of CRP. Further prospective clinical studies are warranted to investigate the effect of treatment of periapical lesions on the glycemic control of diabetic patients and the systemic levels of CRP.

Acknowledgment. *The authors acknowledge the Deanship of Scientific Research, King Abdulaziz University, Jeddah, Kingdom Saudi Arabia for their technical and financial support.*

References

- Kao KT, Sabin MA. Type 2 diabetes mellitus in children and adolescents. *Aust Fam Physician* 2016; 45: 401-406.
- Vega VL, Charles W, Crotty Alexander LE. Rescuing of deficient killing and phagocytic activities of macrophages derived from non-obese diabetic mice by treatment with geldanamycin or heat shock: potential clinical implications. *Cell Stress Chaperones* 2011; 16: 573-581.
- Meo SA. Prevalence and future prediction of type 2 diabetes mellitus in the Kingdom of Saudi Arabia: A systematic review of published studies. *J Pak Med Assoc* 2016; 66: 722-725.
- American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012; 35 Suppl 1: S64-S71.
- Segura-Egea JJ, Castellanos-Cosano L, Machuca G, Lopez-Lopez J, Martin-Gonzalez J, Velasco-Ortega E, et al. Diabetes mellitus, periapical inflammation and endodontic treatment outcome. *Med Oral Patol Oral Cir Bucal* 2012; 17: e356-e361.
- Alzahrani AS, Bissada NF, Jurevic RJ, Narendran S, Nouneh IE, Al-Zahrani MS. Reduced systemic inflammatory mediators after treatment of chronic gingivitis. *Saudi Med J* 2013; 34: 415-419.
- Mukhaimer R, Hussein E, Orafi I. Prevalence of apical periodontitis and quality of root canal treatment in an adult Palestinian sub-population. *Saudi Dent J* 2012; 24: 149-155.
- Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: a two-way relationship. *Br Dent J* 2014; 217: 433-437.
- Nagpal R, Yamashiro Y, Izumi Y. The Two-Way Association of Periodontal Infection with Systemic Disorders: An Overview. *Mediators Inflamm* 2015; 2015: 793898.
- Segura-Egea JJ, Martin-Gonzalez J, Castellanos-Cosano L. Endodontic medicine: connections between apical periodontitis and systemic diseases. *Int Endod J* 2015; 48: 933-951.
- Garber SE, Shabahang S, Escher AP, Torabinejad M. The effect of hyperglycemia on pulpal healing in rats. *J Endod* 2009; 35: 60-62.
- Cintra LT, Samuel RO, Facundo AC, Prieto AK, Sumida DH, Bomfim SR, et al. Relationships between oral infections and blood glucose concentrations or HbA1c levels in normal and diabetic rats. *Int Endod J* 2014; 47: 228-237.
- Segura-Egea JJ, Jimenez-Pinzon A, Rios-Santos JV, Velasco-Ortega E, Cisneros-Cabello R, Poyato-Ferrera M. High prevalence of apical periodontitis amongst type 2 diabetic patients. *Int Endod J* 2005; 38: 564-569.
- Mindiola MJ, Mickel AK, Sami C, Jones JJ, Lalumandier JA, Nelson SS. Endodontic treatment in an American Indian population: a 10-year retrospective study. *J Endod* 2006; 32: 828-832.
- Marotta PS, Fontes TV, Armada L, Lima KC, Rocas IN, Siqueira JE, Jr. Type 2 diabetes mellitus and the prevalence of apical periodontitis and endodontic treatment in an adult Brazilian population. *J Endod* 2012; 38: 297-300.
- Schulze A, Schonauer M, Busse M. Sudden improvement of insulin sensitivity related to an endodontic treatment. *J Periodontol* 2007; 78: 2380-2384.
- Volanakis JE. Human C-reactive protein: expression, structure, and function. *Mol Immunol* 2001; 38: 189-197.
- Belfki H, Ben Ali S, Bougateg S, Ben Ahmed D, Haddad N, Jmal A, et al. Association between C-reactive protein and type 2 diabetes in a Tunisian population. *Inflammation* 2012; 35: 684-689.
- Dehghan A, Kardys I, de Maat MP, Uitterlinden AG, Sijbrands EJ, Bootsma AH, et al. Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes* 2007; 56: 872-878.
- Ticinesi A, Lauretani F, Nouvenne A, Porro E, Fanelli G, Maggio M, et al. C-reactive protein (CRP) measurement in geriatric patients hospitalized for acute infection. *Eur J Intern Med* 2016. pii: S0953-6205(16)30289-8.
- Gomes MS, Blattner TC, Sant'Ana Filho M, Grecca FS, Hugo FN, Fouad AF, et al. Can apical periodontitis modify systemic levels of inflammatory markers? A systematic review and meta-analysis. *J Endod* 2013; 39: 1205-1217.
- Orstavik D, Kerekes K, Eriksen HM. The periapical index: a scoring system for radiographic assessment of apical periodontitis. *Endod Dent Traumatol* 1986; 2: 20-34.
- Kamberi B, Hoxha V, Stavileci M, Dragusha E, Kuci A, Kqiku L. Prevalence of apical periodontitis and endodontic treatment in a Kosovar adult population. *BMC Oral Health* 2011; 11: 32.
- Mesgarani A, Haghanifar S, Eshkevari N, Ehsani M, Khafri S, Nafarzade S, et al. Frequency of odontogenic periradicular lesions in diabetic patients. *Caspian J Intern Med* 2014; 5: 22-25.
- Doyle SL, Hodges JS, Pesun IJ, Baisden MK, Bowles WR. Factors affecting outcomes for single-tooth implants and endodontic restorations. *J Endod* 2007; 33: 399-402.
- Furusho H, Miyouchi M, Hyogo H, Inubushi T, Ao M, Ouhara K, et al. Dental infection of *Porphyromonas gingivalis* exacerbates high fat diet-induced steatohepatitis in mice. *J Gastroenterol* 2013; 48: 1259-1270.
- Chuang FH, Tsai CC, Chen JH, Chen KK, Chen YK, Lin YC. Long-term sequential receptor activator of NF-kappaB ligand (RANKL) and osteoprotegerin (OPG) expression in lipopolysaccharide-induced rat periapical lesions. *J Oral Pathol Med* 2012; 41: 186-193.
- Nassar H, Kantarci A, van Dyke TE. Diabetic periodontitis: a model for activated innate immunity and impaired resolution of inflammation. *Periodontol* 2000 2007; 43: 233-244.
- Lima SM, Grisi DC, Kogawa EM, Franco OL, Peixoto VC, Goncalves-Junior JF, et al. Diabetes mellitus and inflammatory pulpal and periapical disease: a review. *Int Endod J* 2013; 46: 700-709.
- Duarte PM, Miranda TS, Lima JA, Dias Goncalves TE, Santos VR, Bastos MF, et al. Expression of immune-inflammatory markers in sites of chronic periodontitis in patients with type 2 diabetes. *J Periodontol* 2012; 83: 426-434.
- Garcia-Hernandez A, Arzate H, Gil-Chavarria I, Rojo R, Moreno-Fierros L. High glucose concentrations alter the biomineralization process in human osteoblastic cells. *Bone* 2012; 50: 276-288.