Glucose as a Risk Factor for Periodontitis in Kidney Transplantation Patients

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ABSTRACT

Background. Various factors including diabetes and oxidative stress are associated with periodontal inflammation. End-stage renal disease causes various systemic abnormalities in patients, including cardiovascular disaese, metabolic abnormalities, and infection. Even after kidney transplantation (KT), these factors are known to be associated with inflammation. Our study, therefore, aimed to study risk factors associated with periodontitis in KT patients.

Methods. Patients who visited Dongsan Hospital, Daegu, Korea since 2018 and have undergone KT were selected. As of November 2021, 923 participants, with full data including hematologic factors were studied. Periodontitis was diagnosed based on residual bone level in panoramic views. Patients were studied by the presence of periodontitis.

Results. From 923 KT patients, 30 were diagnosed with periodontal disease. Fasting glucose levels were higher in patients with periodontal disease, and total bilirubin levels were lower. When divided by fasting glucose levels, high glucose level showed increase of periodontal disease with odds ratio of 1.031 (95% confidence interval 1.004-1.060). After adjusting for confounders, the results were significant with odds ratio of 1.032 (95% CI 1.004-1.061).

Conclusions. Our study showed that KT patients, of whom uremic toxin clearance has been revolted, are yet at risk of periodontitis by other factors, such as high blood glucose levels.

PATIENTS with end-stage renal disease (ESRD) are constantly exposed to uremic toxins, such as urea, etc. These toxins are known to cause various complications, including periodontal problems in ESRD patients [1−4].

Kidney transplantation (KT) is a treatment for patients with ESRD, which improves survival rate and enhances quality of life by revolting clearance of uremic toxins [5,6]. However, even in KT patients, various oral complications, including periodontitis, are reported to occur [7]. Furthermore, periodontal status and clinical outcomes in KT patients are reported to be related, although mechanisms are unknown [4].

Along with the increase in transplants, there is an increase in side effects of immunosuppressants, including infection, fractures, and malignancy [8,9]. Oral complication includes gingival enlargement in patients treated with cyclosporine A, which is present in 25% to 81% of the patients [10]. Other complications include oral candidiasis, saburral tongue, and Kaposi sarcoma [7,11,12]. More than half of KT patients suffer from one or more oral lesions [11]. Therefore, good oral hygiene and routine care is necessary to reduce patients' burden.

Various factors are reported to be associated with periodontal inflammation. Systemic conditions, such as cardiovascular disease and stroke, have been reported to be associated with periodontal inflammation [13,14]. Other factors include diabetes, oxidative stress, and ESRD [15−17].

To date, no research has been performed to understand factors associated with periodontal disease development in KT patients after removing uremic toxins. Therefore, we studied which factor is associated with periodontitis in patients who have undergone KT.

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MATERIALS AND METHODS

Study Population

The study participants were patients who visited Dongsan Hospital, Daegu, Korea since 2018. As of November 2021, 934 patients had undergone KT. All of the patients were treated with 1.5 to 2.0 g/d of mycophenolate or 1 g intravenously, with maintaining level of tacrolimus in 3 to 8 nmol/mL of blood. All of the patients were ABO matched with donors, and patients with critical transplantation side effects were excluded.

From 934 patients, patients without laboratory data, including aspartate transaminase (AST), alanine transferase, and fasting glucose levels, were excluded from the study. As result, 923 patients were used for the study, of who 30 were diagnosed of periodontal disease. This study was conducted with the approval of Institutional Review Board of Dongsan Hospital, Keimyung University in Korea (IRB No. DSMC 2022-03-006). The study was carried out in accordance with the Declaration of Helsinki and with the term of local legislation.

Data Collection

Laboratory data were collected from blood samples, which were collected after 8 hours of overnight fasting. All of the samples were analyzed on the same day. Blood urea nitrogen, creatinine, albumin, total bilirubin, fasting glucose, white blood cell, red blood cell, hemoglobin, platelet, aspartate transaminase, alanine transferase, alkaline phosphatase, inorganic phosphorus, calcium, total protein, and estimated glomerular filtration rate (eGFR) were obtained by Cobas 8000 c702 (Roche Diagnostics System, Switzerland).

Definition of Renal Functions and Periodontitis

The eGFR was obtained by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, of which the validity was studied elsewhere [18]. Diabetes was defined as fasting glucose of ≥126.

Periodontitis was diagnosed based on residual bone level in panoramic views, according to study of Machado et al [19].

Statistical Analysis

Participants were studied according to diagnosis of periodontal disease. Laboratory data and other confounders were compared between each group, using one-way analysis of variance for continuous variables and χ^2 test for categorical variables. Results were shown as mean ± SD for continuous variables.

Odds ratio (OR) and 95% CI were used to study the relationship between diabetes and periodontal disease. The analyses were adjusted for confounders, which were significantly associated in the analysis, or were profoundly known confounders in other literatures. In Model 1, no confounders were adjusted. In Model 2, age, sex, smoking, aspartate transaminase, alanine transferase, albumin, and eGFR were adjusted. A P value of < .05 was used to indicate statistical significance. All of the analyses were performed by R version 3.5.1 (http://www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 923 KT patients were used for the study: 30 of them were also diagnosed with periodontal disease. The general characteristics of the participants divided by periodontal disease are shown in Table 1. Fasting glucose levels were higher in patients with periodontal disease, and total bilirubin levels were lower. There were no significant differences in age, sex, smoking, and other hematologic factors.

Table 1. Baseline Characteristics of the Participants by Periodontal Disease

	Periodontal Disease (n = 30)	Normal (n = 893)	P
Age, y	56.47 ± 11.07	55.72 ± 11.11	.719
Men, n (%)	18 (60.00%)	537 (60.13%)	1
Smoking, n (%)	3 (10.00%)	37 (4.14%)	.274
BUN	26.60 ± 16.96	22.90 ± 14.71	.178
Creatinine	2.08 ± 2.07	1.47 ± 1.26	.118
AST	20.90 ± 10.56	31.24 ± 241.54	.214
ALT	19.43 ± 19.45	21.49 ± 79.00	.643
ALP	81.90 ± 27.62	80.40 ± 43.43	.777
IP	3.37 ± 0.98	3.34 ± 0.92	.851
Albumin	4.26 ± 0.38	4.26 ± 0.47	.959
Total protein	6.78 ± 0.46	6.69 ± 0.64	.298
Total bilirubin	0.51 ± 0.32	0.67 ± 0.59	.01
WBC	6.50 ± 2.05	7.32 ± 2.81	.042
RBC	4.13 ± 0.87	4.37 ± 0.81	.121
Hb	12.40 ± 2.08	13.13 ± 2.37	.092
Hct	37.75 ± 6.09	39.89 ± 6.88	.092
Platelet	214.87 ± 65.52	220.24 ± 66.64	.664
Calcium	9.48 ± 0.67	9.53 ± 0.77	.729
Glucose	134.93 ± 53.86	116.36 ± 47.44	.036
eGFR	55.76 ± 28.39	63.56 ± 24.46	.088

Data were expressed as mean ± SD for continuous variables and n (%) for categorical variables.

ALT, alanine transferase; ALP, alkaline phosphatase; AST, aspartate transaminase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Hct, hematocrit; IP, inorganic phosphorus; RBC, red blood cell; WBC, white blood cell.

Table 2 shows association between fasting glucose, divided by 126 mg/dL. Compared with low glucose level, high glucose level showed increase of periodontal disease with OR of 1.031 (95% CI 1.004-1.060). After adjusting for confounders, the results were significant with OR 1.032 (95% CI 1.004-1.061).

DISCUSSION

Our study has shown that high fasting glucose levels are associated with periodontal disease in KT patients. The results were consistent after adjusting for confounding factors.

End-stage renal disease is characterized by structural changes in the renal system, causing uremia by reducing filtration abilities [20]. Uremia causes various abnormalities, including cardiovascular disease, metabolic abnormalities, and infection due to leukocyte dysfunction [21]. Furthermore, uremia is the cause

Table 2. Odds Ratios of Periodontal Disease According to Diabetes

	Model 1 OR (95% CI)	P	Model 2 OR (95% CI)	P
Diabetes	1.031 (1.004-1.060)	< .05	1.032 (1.004-1.061)	< .05

Model 1: not adjusted; Model 2: adjusted for age, gender, smoking, aspartate transaminase, alanine transferase, albumin, and estimated glomerular filtration rate.

OR, odds ratio.

of several dental problems, including xerostomy, uremic stomatitis, and dental calculus formation [22]. Periodontal disease also is linked to ESRD, according to several studies [23−25]. Therefore, the current study aimed to assess risk factors associated with periodontal disease in ESRD patients who have undergone KT.

Periodontal disease and diabetes are known to have bidirectional effects, with a higher percentage of diabetes to be higher in patients with periodontal disease compared with healthy patients [26]. Mechanisms involved include inflammatory cytokines and oxidative stress [27]. Also, poor leukocyte function is known to be involved in periodontal disease [28]. However, the association between periodontal disease and transplantation has not been studied. However, several factors have been reported to be associated with periodontal inflammation in KT patients. Smoking, diabetes, and cardiovascular disease have been reported to be associated with periodontal inflammation [13,15,29]. Another factor, eGFR, was not significant in our study [17]. Diabetes is suspected to increase susceptibility of disease via altering gingival flora, and increase in oxidative stress [18,30]. This might have caused the association of glucose and periodontal disease in transplantations in our study.

Our study was a cross-sectional study lacking follow-up. Therefore, long-term effects of glucose levels on periodontal disease are yet to be studied. Furthermore, as data were collected retrospectively, additional survey data, such as oral hygiene and care, are absent. Further studies should be performed to adjust its effects. Future studies should be performed to understand long-term relationship between glucose and periodontitis. Especially, HbA1c, which shows the average status of glucose levels of the past 3 months, should be used in future studies. Also, as the current study has studied only periodontitis by disease code given from the hospital, further data using periodontal inflamed surface area levels are suggested in future studies.

Our study has shown that KT patients, of whom uremic toxin clearance has been revolted, are yet at risk of periodontitis by other factors, such as high blood glucose levels.

DATA AVAILABILITY

Data will be made available on request.

DISCLOSURE

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

[1] Kirkman DL, Roberts LD, Kelm M, et al. Interaction between intradialytic exercise and hemodialysis adequacy. Am J Nephrol 2013;38:475–82.

[2] Kirkman DL, Scott M, Kidd J, et al. The effects of intradialytic exercise on hemodialysis adequacy: a systematic review. Semin Dial 2019;32:368–78.

[3] Koppe L, Fouque D, Soulage CO. Metabolic abnormalities in diabetes and kidney disease: role of uremic toxins. Curr Diab Rep 2018;18:97.

[4] Nunes-Dos-Santos DL, Gomes SV, Rodrigues VP, et al. Periodontal status and clinical outcomes in kidney transplant recipients: A systematic review. Oral Dis 2020;26:22–34.

[5] Kim MH, Kim MS, Kwon OJ, et al. Comparison of quality of life between kidney transplant patients and dialysis patients. J Korean Soc Transplant 2009;23:65–70.

[6] Ju A, Chow BY, Ralph AF, et al. Patient-reported outcome measures for life participation in kidney transplantation: a systematic review. Am J Transplant 2019;19:2306–17.

[7] López-Pintor RM, Hernández G, de Arriba L, et al. Oral candidiasis in patients with renal transplants. Med Oral Patol Oral Cir Bucal 2013;18:381–7.

[8] Andreś A. Cancer incidence after immunosuppressive treatment following kidney transplantation. Crit Rev Oncol Hematol 2005;56:71–85.

[9] Stucker F, Ackermann D. Immunosuppressive drugs-how they work, their side effects and interactions. Ther Umsch 2011;68:679–86.

[10] Romito GA, Pustiglioni FE, Saraiva L, et al. Relationship of subgingival and salivary microbiota to gingival overgrowth in heart transplant patients following cyclosporin A therapy. J Periodontol 2004;75:918–24.

[11] de la Rosa-Garcia E, Mondragon-Padilla A, Irigoyen-Camacho ME, et al. Oral lesions in a group of kidney transplant patients. Med Oral Patol Oral Cir Bucal 2005;10:196–204.

[12] Bubić-Filipi L, Bašić-Jukić N, Pasini J, et al. Clinical features of Kaposi's sarcoma in Croatian renal transplant recipients. Prilozi 2009;30:175–84.

[13] Bahekar AA, Singh S, Saha S, et al. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. Am Heart J 2007;154:830–7.

[14] Desvarieux M, Demmer RT, Rundek T, et al. Relationship between periodontal disease, tooth loss, and carotid artery plaque: The oral infections and vascular disease epidemiology study (INVEST). Stroke 2003;34:2120–5.

[15] Lamster IB, Lalla E. Periodontal disease and diabetes mellitus: discussion, conclusions, and recommendations. Ann Periodontol 2001;6:146–9.

[16] Allen EM, Matthews JB, Halloran DJO, et al. Oxidative and inflammatory status in Type 2 diabetes patients with periodontitis. J Clin Periodontol 2011;38:894–901.

[17] Deschamps-Lenhardt S, Martin-Cabezas R, Hannedouche T, et al. Association between periodontitis and chronic kidney disease: systematic review and meta-analysis. Oral Dis 2018;25:385–402.

[18] Buranasin P, Mizutani K, Iwasaki K, et al. High glucose-induced oxidative stress impairs proliferation and migration of human gingival fibroblasts. PLoS One 2018;13:e0201855.

[19] Machado V, Proença L, Morgado M, et al. Accuracy of panoramic radiograph for diagnosing periodontitis comparing to clinical examination. J Clin Med 2020;9:2313.

[20] Pallos D, Leão MVP, Togeiro FCFB, et al. Salivary markers in patients with chronic renal failure. Arch Oral Biol 2015;60:1784–8.

[21] Cohen G, Hörl WH. Immune dysfunction in uremia—an update. Toxins 2012;4:962–90.

[22] de Souza Dias CR, de Sá TCV, Pereira ALA, et al. Evaluation of oral condition of patients with chronic renal failure submitted to hemodialysis. Rev Assoc Med Bras 2007;53:510–4.

[23] Liu K, Liu Q, Chen W, et al. Prevalence and risk factors of CKD in Chinese patients with periodontal disease. PLoS One 2013;8:e70767.

[24] Davidovich E, Schwarz Z, Davidovitch M, et al. Oral findings and periodontal status in children, adolescents and young adults suffering from renal failure. J Clin Periodontol 2005;32:1076–82.

[25] Marakoglu I, Gursoy UK, Demirer S, et al. Periodontal status of chronic renal failure patients receiving hemodialysis. Yonsei Med J 2003;44:648–52.

[26] Ziukaite L, Slot DE, Van der Weijden FA. Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: a systematic review and meta-analysis of epidemiologic studies. J Clin Periodontol 2018;45:650–62.

[27] Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther 2012;30:49–59.

[28] Mauri-Obradors E, Estrugo-Devesa A, Jané-Salas E, et al. Oral manifestations of diabetes mellitus. A systematic review. Med Oral Patol Oral Cir Bucal 2017;22:e586–94.

[29] Ship JA. Diabetes and oral health: an overview. J Am Dent Assoc 2003;134:4S–10S.

[30] Indurkar MS, Maurya AS, Indurkar S. Oral manifestations of diabetes. Clin Diabetes 2016;34:54–7.