



The effect of periodontitis on recipient outcomes after kidney transplantation

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Background: Recent several reports have demonstrated that periodontitis is prevalent and adversely affects the survival in patients with chronic kidney disease (CKD) or end-stage kidney disease. However, its impact on transplant outcomes remains uncertain.

Methods: This retrospective cohort study included 136 and 167 patients, respectively, who underwent living donor kidney transplantation (KT) at Seoul National University Hospital from July 2012 to August 2016 and Korea University Hospital from April 2008 to October 2018. We divided patients into three groups according to stages of periodontitis based on a new classification system.

Results: Patients with severe periodontitis were older, had a higher prevalence of diabetes, a higher body mass index and C-reactive protein level, a lower cardiac output, and were more likely to be smokers, indicating its association with chronic systemic inflammation. After KT, stage IV periodontitis was independently associated with a lower incidence of acute T cell-mediated rejection, suggesting the possible effect of periodontitis on immune function. However, 1-year and 3-year estimated glomerular filtration rates were not different. Among the KT recipients followed up more than 3 years, new-onset cardiovascular disease occurred in nine patients, and coronary artery disease occurred more frequently in patients with stage IV periodontitis. However, diabetes was the independent predictor of new-onset coronary artery disease in multivariate logistic regression analysis.

Conclusion: Our findings showed that periodontitis might be an important player in determining posttransplant outcomes in recipients. Further interventional trials to test whether treating periodontitis could modify transplant outcome are needed.

Keywords: Cardiovascular diseases, Graft rejection, Kidney transplantation, Periodontitis

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Introduction

Periodontitis, an inflammatory condition that affects the tissues around teeth, is one of the most common oral diseases, and severe periodontal inflammation can damage soft tissues and destroy the bones that support the teeth [1]. Moreover, periodontitis is associated not only with oral health but also with the development and exacerbation of various systemic diseases [2]. Recent studies have shown that periodontitis is common in patients with advanced chronic kidney disease (CKD) and contributes to systemic inflammation, infection, malnutrition, and atherosclerotic disease, which can increase morbidity and mortality in CKD [3–6].

As in patients with CKD, periodontitis may be an important factor that affects graft function and recipient outcomes in kidney transplantation (KT) patients. Long-term immunosuppression of KT recipients is a major factor in the development of posttransplant complications, including new metabolic burdens, cardiovascular disease (CVD), infections, and malignancies. Poor oral health also can affect chronic inflammation, immune function, and metabolic complications, so it may play an important role in recipient outcomes. Previous studies of KT recipients have shown that periodontitis can be associated with high levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 and negatively affect graft function [7]. However, most studies included fewer than 100 patients, and each study produced conflicting results regarding post-KT complications.

Because oral health affects systemic health and has been proposed as a possible target for the treatment of various systemic diseases [8], it is important to determine the impact of oral diseases on grafts and systemic health of KT recipients. The aim of this study, therefore, was to examine whether periodontitis before KT affects posttransplant outcomes.

Methods

Study design and patients

This was a retrospective cohort study including adolescent and adult patients aged 16 to 68 years who underwent living donor KT in two tertiary medical hospitals (Korea

University Anam Hospital and Seoul National University Hospital in Seoul, Republic of Korea). We included 136 patients who received KT from July 2012 to August 2016 at Seoul National University Hospital and 167 patients who received KT from April 2008 to October 2018 at Korea University Hospital. The study protocol was approved before study initiation by the Institutional Review Boards (IRBs) of Korea University Anam Hospital (No. K2018-2287-001) and Seoul National University Hospital (No. H-1904-142-1029) and was conducted according to the Declaration of Helsinki guidelines. IRBs waived the need to obtain informed consent because the study was retrospective and required no deviation from routine medical practice.

Demographic data (sex, age, smoking history) and clinical features (comorbidities, body mass index [BMI], cause of the end-stage kidney disease (ESKD), renal replacement therapy and laboratory data, including creatinine, hemoglobin, albumin, CRP ($10 \times$ high sensitivity CRP [hsCRP]; hsCRP of Seoul National University Hospital converted to CRP of Korea University Medical Center with a conversion factor by Milone et al. [9]), lipid profile, calcium, and phosphate, among others) were obtained from the electronic medical records system. Panoramic X-ray was performed for pre-KT dental examination and analyzed retrospectively by two periodontists for periodontal grading according to the new classification of periodontal diseases developed in 2017 by Tonetti et al. [10]. Radiographic alveolar bone loss and tooth loss were primarily used to assess the severity of periodontitis and determine the stage of individual periodontitis.

Allograft function was assessed at 1, 12, and 36 months using the serum creatinine concentration and glomerular filtration rate (GFR), which was calculated using the Modification of Diet in Renal Disease Study (MDRD) GFR equations. A kidney biopsy was performed to assess the cause of acute kidney injury, and rejection was diagnosed based on histologic examination and classified into acute antibody-mediated rejection (AMR), acute T cell-mediated rejection (ATMR) by Banff 2017 classifications. Bacterial infection was defined based on hospitalization and antibiotic administration, and BK and cytomegalovirus (CMV) viremia were evaluated. CVD included cerebrovascular disease and acute coronary artery disease defined as new-onset unstable angina or acute myocardial infarction.

Immunologic characteristics

Simulect or thymoglobulin was used as an induction immunosuppressive agent. After induction therapy, the initial maintenance immunosuppressant was either a tacrolimus-based (tacrolimus + mycophenolate, tacrolimus + sirolimus, tacrolimus + bredinin) or cyclosporine-based (cyclosporine + mycophenolate) regimen. Blood concentration of immunosuppressive agent was assayed every visit as routine and adequate doses of calcineurin inhibitors were adjusted to maintain their reference values.

Statistical analysis

IBM SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses. Categorical variables were analyzed using the linear by linear test. Summaries of the continuous variables are expressed as median and standard deviation. The analysis of variance was used to analyze continuous variables. Multivariate logistic regression analyses were performed to evaluate the effect of multiple independent predictors. In this model, a backward stepwise selection approach was adopted. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics before kidney transplantation

During the study period, a total of 303 recipients who underwent pre-KT dental examinations were included. Patients were divided into three groups according to the stage of periodontitis: mild, stage I and II (n = 160, 52.8%); severe, stage III (n = 89, 29.4%); and advanced, stage IV (n = 54, 17.8%). The demographic and baseline characteristics of the 303 patients are listed in [Table 1](#). Of them, 205 patients (67.7%) were male, and 36 (11.9%) were current smokers. The median age of recipients and donors was 43.97 ± 12.28 and 45.86 ± 10.92 years, respectively. Sixty patients (19.8%) had diabetes mellitus, 75 (24.8%) had hypertension, 85 (28.1%) had glomerulonephritis, and 15 (5.0%) had polycystic kidney disease as the cause of ESKD. In patients with stage I and II periodontitis, glomerulonephritis was the main cause of ESKD, but in patients with stage IV periodontitis, diabetes was the major cause. The most common form of renal replacement therapy was hemodialysis (n =

201, 66.3%), and preemptive KT was performed more frequently in patients with mild stage periodontitis. The main comorbidities of patients with periodontitis before KT were hypertension (n = 272, 89.8%), followed by dyslipidemia (n = 185, 61.1%) and diabetes (n = 73, 24.1%). Patients with stage III or IV periodontitis were older, had a higher prevalence of diabetes, a higher BMI, a lower left ventricular ejection fraction, a higher CRP level, and were more likely to be current smokers ([Table 1](#); [Supplementary Table 1](#), available online). There were no significant differences in the number of human leukocyte antigen (HLA) mismatches and the use of immunosuppressants between the groups ([Table 2](#)).

Transplant outcomes

Clinical outcomes of patients with periodontitis are shown in [Table 3](#). During the follow-up period, AMR occurred in 18 patients, while ATMR or borderline ATMR occurred in 113 patients, respectively. In multivariate logistic regression analysis, stage IV periodontitis and the number of HLA mismatches were independent factors associated with the development of ATMR after KT ([Table 4](#)). Subgroup analysis also showed that an independent effect of advanced periodontitis on ATMR was observed only in pre-KT dialysis patients but not in preemptive KT patients (data not shown). Although the rate of ATMR was

significantly lower in patients with stage IV periodontitis, there were no differences in estimated GFR (eGFR) at 1 month, 1 year, and 3 years or eGFR loss from 1 month according to different stages of periodontitis ([Table 3](#)). In addition, the degree of periodontitis did not predict graft failure significantly ([Supplementary Fig. 1](#), available online). Bacterial infections, including pneumonia, urinary tract infection, and bacteremia, were diagnosed in 71 patients, and CMV and BK viremia were detected in 43 and 53 patients, respectively. However, there was no significant difference in the incidence of bacterial infection, CMV and BK viremia according to different stages of pretransplant periodontitis ([Table 3](#)).

Cardiovascular outcomes were analyzed in patients who were sufficiently followed up after KT. In the patients with a follow-up period of 3 years or more, new coronary artery disease developed in eight patients and cerebrovascular disease developed in one. Coronary artery disease oc-

Table 1. Baseline characteristics of recipients with periodontitis before kidney transplantation

Characteristic	Total	Stage I and II	Stage III	Stage IV	p-value
Patient	303 (100)	160 (52.8)	89 (29.4)	54 (17.8)	
Age (yr)	43.97 ± 12.28	39.04 ± 12.13	48.17 ± 10.46	51.69 ± 8.50	<0.001
Male sex	205 (67.7)	103 (64.4)	64 (71.9)	38 (70.4)	0.28
Body mass index (kg/m ²)	23.28 ± 3.75	22.44 ± 3.70	23.74 ± 3.24	25.01 ± 4.02	<0.001
Current smoker	36 (11.9)	14 (8.8)	9 (10.1)	13 (24.1)	0.008
Causes of ESKD					
Diabetes mellitus	60 (19.8)	18 (11.3)	19 (21.3)	23 (42.6)	<0.001
Hypertension	75 (24.8)	30 (18.8)	31 (34.8)	14 (25.9)	0.08
Glomerulonephritis	85 (28.1)	62 (38.8)	16 (18.0)	7 (13.0)	<0.001
Polycystic kidney disease	15 (5.0)	10 (6.3)	5 (5.6)	0 (0)	0.10
Others	16 (5.3)	15 (9.4)	0 (0)	1 (1.9)	0.005
Unknown	52 (17.2)	25 (15.6)	18 (20.2)	9 (16.7)	0.66
Renal replacement therapy					
Hemodialysis	201 (66.3)	98 (61.3)	60 (67.4)	43 (79.6)	0.02
Peritoneal dialysis	49 (16.2)	27 (16.9)	17 (19.1)	5 (9.3)	0.32
Preemptive	53 (17.5)	35 (21.9)	12 (13.5)	6 (11.1)	0.04
Dialysis vintage (mo)	14.94 ± 25.80	14.19 ± 22.87	17.09 ± 30.33	13.53 ± 26.02	0.67
Comorbidity					
Hypertension	272 (89.8)	143 (89.4)	83 (93.3)	46 (85.2)	0.20
Diabetes mellitus	73 (24.1)	22 (13.8)	25 (28.1)	26 (48.1)	<0.001
Dyslipidemia	185 (61.1)	93 (58.1)	54 (60.7)	38 (70.4)	0.14
Ejection fraction of heart	57.26 ± 7.19	58.32 ± 6.77	56.35 ± 6.76	55.54 ± 8.67	0.02
Laboratory test					
Hemoglobin (g/dL)	10.43 ± 1.68	10.44 ± 1.63	10.50 ± 1.88	10.29 ± 1.51	0.76
Albumin (g/dL)	3.95 ± 0.49	4.00 ± 0.48	3.90 ± 0.51	3.90 ± 0.48	0.23
CRP (mg/L), 10 × hsCRP ^a	4.88 ± 15.41	2.80 ± 5.79	5.74 ± 15.07	9.68 ± 28.93	0.01
LDL cholesterol (mg/dL)	85.13 ± 30.47	84.70 ± 32.57	83.13 ± 28.67	89.62 ± 26.88	0.46
Triglyceride (mg/dL)	125.95 ± 85.88	124.59 ± 78.57	125.51 ± 90.30	130.62 ± 99.28	0.91
Calcium (mg/dL) × phosphate (mg/dL)	47.96 ± 16.42	47.24 ± 16.45	49.57 ± 16.44	47.42 ± 16.42	0.55
iPTH (pg/mL)	250.66 ± 246.75	256.21 ± 284.45	243.97 ± 208.09	245.48 ± 182.61	0.92
Donor age (yr)	45.86 ± 10.92	46.21 ± 10.50	45.99 ± 11.37	44.63 ± 11.52	0.65

Data are expressed as number (%) or mean ± standard deviation.

CRP, C-reactive protein; ESKD, end-stage kidney disease; hsCRP, high sensitivity CRP; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein.

^ahsCRP of Seoul National University Hospital converted to CRP of Korea University Medical Center with a conversion factor (10) by method of Milone et al. [9].

occurred more frequently in patients with stage IV periodontitis (Table 5). However, diabetes was the strongest independent predictor of new-onset coronary artery disease in multivariate logistic regression analysis (Table 6).

Discussion

It has long been questioned whether poor oral health is associated with systemic diseases. Epidemiologic studies have reported that poor oral conditions, such as periodontitis or gingivitis, are associated with the development of

various systemic diseases, such as atherosclerosis, diabetes, respiratory disease, rheumatoid disease, and complicated pregnancy [11]. Several pathways, such as systemic inflammation due to direct metastatic spread of pathogenic bacteria from the oral cavity or indirect effects of circulating microbial products and immunologic modulation, have been proposed to link periodontitis with systemic diseases [12,13].

Periodontitis is common in patients with CKD, and some studies have shown that CKD patients with periodontitis have lower eGFR, higher morbidity and mortality com-

Table 2. Immunologic characteristic of recipients with periodontitis

Variable	Total	Stage I and II	Stage III	Stage IV	p-value
No. of HLA mismatch	3.39 ± 1.57	3.19 ± 1.61	3.61 ± 1.60	3.63 ± 1.32	0.06
Induction immunosuppressive agent					
Simulect ^a	263 (86.8)	143 (89.4)	76 (85.4)	44 (81.5)	0.12
Maintenance immunosuppressive agent (initial)					
Tacrolimus-based regimen ^b	285 (94.1)	150 (93.8)	82 (92.1)	53 (98.1)	0.26
Maintenance immunosuppressive agent (at 1 yr)					
Tacrolimus-based regimen	249 (91.5)	131 (92.3)	71 (88.7)	47 (94.0)	0.95
Tacrolimus + mycophenolate	207 (76.1)	105 (73.9)	60 (75.0)	42 (84.0)	0.20
Tacrolimus + sirolimus	27 (9.9)	16 (11.3)	9 (11.3)	2 (4.0)	0.20
Tacrolimus + bredinin	15 (5.5)	10 (7.0)	2 (2.5)	3 (6.0)	0.51
Cyclosporine + mycophenolate	23 (8.5)	11 (7.7)	9 (11.3)	3 (6.0)	0.95

Data are expressed as mean ± standard deviation or number (%).

HLA, human leukocyte antigen.

^aSimulect or anti-thymocyte globulin were used as induction immunosuppressive agent. ^bInitial maintenance immunosuppressive agent was tacrolimus- or cyclosporine-based regimen.

Table 3. Clinical outcome of patients with periodontitis after KT

Variable	Total (n = 303)	Stage I and II (n = 160)	Stage III (n = 89)	Stage IV (n = 54)	p-value
GFR (mL/min/1.73 m ²)					
1-Month GFR	69.82 ± 19.91	69.71 ± 20.50	70.12 ± 17.73	69.62 ± 21.83	0.99
1-Year GFR ^a	65.67 ± 16.96	64.68 ± 18.50	67.19 ± 12.61	66.43 ± 18.03	0.56
3-Year GFR ^b	67.31 ± 17.71	67.07 ± 19.76	67.96 ± 13.41	67.14 ± 14.55	0.95
Rejection					
AMR	18 (5.9)	9 (5.6)	4 (4.5)	5 (9.3)	0.47
ATMR or borderline ATMR	113 (37.3)	69 (43.1)	31 (34.8)	13 (24.1)	0.01
Graft loss	14 (4.6)	7 (4.4)	4 (4.5)	3 (5.6)	0.75
Infection					
Bacterial infection	71 (23.4)	39 (24.4)	19 (21.3)	13 (24.1)	0.84
CMV viremia	43 (14.2)	20 (12.5)	17 (19.1)	6 (11.1)	0.82
BK viremia	53 (17.5)	33 (20.6)	15 (16.9)	5 (9.3)	0.06

Data are expressed as mean ± standard deviation or number (%).

AMR, acute antibody-mediated rejection; ATMR, acute T cell-mediated rejection; CMV, cytomegalovirus; GFR, glomerular filtration rate; KT, kidney transplantation.

^aA total of 262 patients who followed up for more than 1 year after KT were included. ^bA total of 202 patients who followed up for more than 3 years after KT were included.

pared to those without periodontitis; however, conflicting results have also been reported [4,14,15]. Because patients with CKD already have several comorbid conditions that affect systemic inflammation, it is possible that these comorbid conditions affect both oral health and CKD outcomes. Therefore, it is difficult to clarify the direct link between periodontitis and CKD outcomes. Nevertheless, a recent study showed that the risk of developing CVDs over 24 months was lower in patients with CKD treated with periodontal disease, which suggests an important role of

periodontitis in cardiovascular outcomes of patients with CKD [16].

Like previous studies, we found that patients with severe periodontitis prior to KT were older, more diabetic, had a higher BMI, and had a lower ejection fraction, showing that periodontitis is also closely linked to systemic inflammation, metabolic complications, and CVDs. We hypothesized that periodontitis, a chronic inflammatory condition, might skew the short and long-term transplant outcomes. This was based on the fact that chronic inflammation is

Table 4. Risk factors to predict acute T cell-mediated rejection

Variable	Crude model		Age, sex-adjusted model		Multivariate model	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (female)	0.69 (0.42–1.16)	0.16				
Age (yr)	0.98 (0.96–0.99)	0.04				
Year of KT	1.11 (0.99–1.25)	0.06	1.13 (1.01–1.27)	0.03		
Donor age (yr)	1.03 (1.00–1.05)	0.03	1.02 (1.00–1.05)	0.04		
HLA mismatch	1.15 (0.99–1.34)	0.07	1.23 (1.05–1.45)	0.01	1.39 (1.10–1.77)	0.006
Relationship						
Unrelated	1.62 (0.98–2.68)	0.06	2.02 (1.17–3.47)	0.01		
Induction IS						
ATG	0.38 (0.17–0.85)	0.38	0.38 (0.17–0.86)	0.02		
Maintenance IS at 1 yr						
Tacrolimus-based	1.00		1.00			
CsA-based	2.60 (0.90–7.54)	0.08	2.47 (0.84–7.24)	0.10		
CMV viremia	1.56 (0.82–3.00)	0.18	1.55 (0.80–3.00)	0.19		
CRP (mg/L), 10 x hsCRP	0.97 (0.94–1.01)	0.09	0.9 (0.93–1.00)	0.06		
HbA1c (% of THb)	0.84 (0.61–1.16)	0.29	0.90 (0.66–1.24)	0.53		
Periodontitis						
Stage I and II	1.0		1.00		1.00	
Stage III	0.71 (0.41–1.21)	0.20	0.77 (0.43–1.36)	0.36	1.42 (0.59–3.41)	0.44
Stage IV	0.42 (0.21–0.84)	0.01	0.48 (0.23–1.01)	0.05	0.28 (0.08–0.98)	0.05

ATG, anti-thymocyte globulin; CI, confidence interval; CMV, cytomegalovirus; CRP, C-reactive protein; CsA, cyclosporine; HbA1c, hemoglobin A1c; IS, immunosuppressant; KT, kidney transplantation; OR, odds ratio.

In the age, sex-adjusted model, an enter selection approach was adopted. In the multivariate logistic analysis model, age, male sex, donor age, CRP, number of human leukocyte antigen mismatch, relationship, year of KT, induction immunosuppressive agent, maintenance immunosuppressive agent at 1 year, stage of periodontitis were adjusted. Multivariate logistic regression was performed with variables with p-value less than 0.3 in univariate analysis; a backward stepwise selection approach was adopted. All laboratory data were examined prior to KT.

Table 5. Cardiovascular diseases in patients with a follow-up period of 3 years or more

Variable	Total (n = 202)	Stage I and II (n = 127)	Stage III (n = 52)	Stage IV (n = 23)	p-value
Cardiovascular disease	9 (4.5)	3 (2.4)	2 (3.8)	4 (17.4)	0.006
Coronary artery disease ^a	8 (4.0)	3 (2.4)	2 (3.8)	3 (13.0)	0.03
Cerebrovascular disease	1 (0.5)	0 (0)	0 (0)	1 (4.3)	0.03

Data are presented as number (%).

^aCoronary artery disease: unstable angina, myocardial infarction.

a well-known risk factor of CVDs as well as an impaired adaptive immune response [17]. Given that transplant recipients are confronting the very complex immunologic and nonimmunologic challenges including the use of potent immunosuppressants, reduction of uremic burden or better nutrition and potential changes of oral microbiome, the effect of chronic periodontitis on various transplant outcomes could be more complicated.

Interestingly, we first observed that the rate of ATMR was significantly lower in patients with severe periodontitis. The effect of periodontitis on acute rejection is still unknown. A

previous study showed that periodontitis increases the risk of acute rejection [18], but the cross-sectional study design makes it difficult to rule out the possibility that periodontitis was exacerbated due to immunosuppressive treatment during acute rejection. Considering that T cells are the main players mediating acute rejection, it is possible that pretransplant periodontitis led to defective T cell immunity such as T cell exhaustion, which may have preventive effect on early T cell-mediated rejection. The link between chronic inflammation and impaired immunity has been demonstrated in the inflammation area. Uneven homeo-

Table 6. Risk factors to predict new-onset coronary artery disease

Variable	Crude model		Multivariate model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female sex	0.31 (0.04–2.59)	0.28		
Age (yr)	1.02 (1.00–1.17)	0.04		
Year of KT	1.13 (0.74–1.71)	0.58		
HbA1c (% of THb)	1.35 (0.83–2.18)	0.23		
Donor age (yr)	0.95 (0.89–1.01)	0.09		
Ca (mg/dL)	1.54 (0.66–3.59)	0.32		
iPTH (pg/mL)	0.997 (0.99–1.00)	0.24		
Body mass index	1.09 (0.90–1.32)	0.37		
Dyslipidemia	1.49 (0.36–6.12)	0.58		
Causes of ESKD				
Diabetes mellitus	7.07 (1.62–30.93)	0.009	4.73 (1.08–20.77)	0.04
Glomerulonephritis	0.26 (0.03–2.15)	0.21		
Periodontitis stage				
Stage I and II	1.00			
Stage III	1.65 (0.27–10.20)	0.59		
Stage IV	6.20 (1.17–32.89)	0.03		

CI, confidence interval; ESKD, end-stage kidney disease; iPTH, intact parathyroid hormone; KT, kidney transplantation; OR, odds ratio.

In the multivariate logistic analysis model, age, male sex, donor age, hemoglobin A1c, iPTH, cause of end-stage renal disease (diabetes mellitus, glomerulonephritis), year of KT, stage of periodontitis were adjusted. Multivariate logistic regression was performed with variables with p-value less than 0.3 in univariate analysis; a backward stepwise selection approach was adopted. All laboratory data were examined prior to KT. Dyslipidemia was defined as those with low-density lipoprotein cholesterol greater than 100 mg/dL or triglyceride greater than 500 mg/dL or under lipid-lowering agent.

static proliferation of naïve T cells in thymectomized mice [19], as well as reduced T cell priming upon vaccination in ESKD patients [20], suggest that chronic inflammation is closely linked to both quantitative and qualitative defect of T cell immunity. Recent studies have suggested that chronic periodontitis is associated with an immunomodulatory profile by observing the upregulation of Th1 cytokines in early periodontitis and Th2 cytokines in later stages [21].

The relationship between immune-senescence and chronic periodontitis has also been reported. Steffens et al. [22] demonstrated that chronic inflammatory burden observed in patients with chronic periodontitis could accelerate leukocyte telomere shortening, which may indicate impaired immune function. Masi et al. [23] also reported that the leukocyte telomere length was negatively correlated with severity of periodontitis, suggesting that shorter telomere lengths correlate with oxidative stress, chronic inflammation, and severity of disease. Interestingly, the independent effect of advanced periodontitis on ATMR was observed only in pre-KT dialysis patients and not in pre-emptive KT patients, suggesting that the chronic inflammatory status of pretransplant dialysis patients may modify

not only periodontitis itself but also the effect of periodontitis on immune function.

Several studies have shown that periodontitis was associated with poor graft function [24]. However, because most were cross-sectional studies, it is difficult to identify causality, and some small transplant cohort studies reported opposite results regarding the relationship between oral health and graft function [25]. T cell-mediated rejection is a well-known cause of early graft dysfunction and many studies indicate the early dysfunction might lead to poor long-term graft outcomes [26,27]. However, despite significantly lower rate of ATMR in patients with severe periodontitis, we found that eGFR at 1 month, 1 year, and 3 years after KT were not different according to stages of periodontitis. In addition, the severity of periodontitis did not significantly predict graft failure. These results suggest that periodontitis can have a complex effect on graft function by multiple factors, such as chronic inflammation and CVD, as well as a favorable effect on rejection.

CVD after KT is a major factor in determining graft and patient survival and is still an important barrier to improving the long-term outcomes of KT recipients [28]. Exposure

to various traditional (hypertension, dyslipidemia, diabetes, smoking, and obesity) and nontraditional risk factors affect CVD development after KT. Therefore, to improve KT outcomes, it is important to identify high-risk recipients and initiate early risk-reduction strategies. Poor oral health has recently been proposed as a possible nontraditional risk factor of CVD in patients with CKD, but few studies were performed in patients with KT. In 2007, Genctoy et al. [29] reported that KT patients with severe gingivitis had a higher carotid intima-media thickness than those without gingivitis. Although this study had a cross-sectional design, gingivitis in transplant recipients affected the development and/or progression of atherosclerosis despite the unclear role of gingivitis in systemic inflammation. However, in a recent longitudinal study, periodontitis did not significantly increase the incidence of major adverse cardiovascular episodes [30]. In our study, followed by a large number of patients for more than 3 years, severe periodontitis was associated with the incidence of new-onset coronary artery disease, whereas diabetes was the only independent risk factor in the multivariate analysis. Because the incidence of CVD was relatively lower in our study, further investigation in a large cohort is warranted to assess the independent effects of periodontitis on cardiovascular events and mortality after KT.

For posttransplant infection, which is the leading cause of hospitalization of transplant recipients, possible T cell immune dysfunction following periodontitis may leave the host vulnerable to infections; however, bacterial infection, CMV, and BK viremia did not show any significant association with periodontitis. The innate immune response to bacterial or viral invasion, as well as the adaptive immune response through T and B cells, plays an important role in infection-related complications; therefore, various confounding factors besides periodontitis can contribute to the development of posttransplant infection.

Despite several novel findings, our study has several limitations. First, the design of the study was retrospective, and the treatment of periodontitis was not investigated in detail as there were some cases where treatment was performed at other hospitals. Therefore, it was difficult to clearly understand the causal relationship between periodontitis and posttransplant outcomes. Second, we have not presented laboratory evidence showing the relationship between periodontitis and immune dysfunction. In addition, tradi-

tional risk factors for posttransplant CVD, such as steroid dose, concentration of calcineurin inhibitor, posttransplant diabetes, hypertension, and economic status, have not been analyzed in detail.

However, strength of our study lies in the fact that cases of severe periodontitis were especially sorted out by new staging system and were separately analyzed. Community Periodontal Index of Treatment Needs (CPITN) or other indices in previous studies reflect the extent of periodontitis that is potentially responsive to treatment rather than chronic or irreversible conditions. But this new system includes radiographic bone loss as one of the parameters to be considered in severity determinations, and additional ideas such as treatment complexities and prognosis assessment are also conveyed in stage itself. In particular, stage III and IV patients of the new system may present severe cases with additional risk factors besides periodontal bacterial deposition, such as chronic systemic inflammatory conditions, alveolar bone resorption, and loss of immune defenses against bacterial infection [31,32]. Therefore, these differences may provide additional information on impaired immune response in our study.

Recently, the role of the immune system has been noted as an important factor in bone destruction [33], the degree of alveolar bone loss depends on the host response against oral infection. Our results suggest that amount of alveolar bone loss due to chronic inflammation before KT reflects systemic inflammatory conditions and altered immune function, and is an important factor affecting transplant outcomes beyond oral inflammation.

In conclusion, even in a new immunological and metabolic environment with reduced uremic burden and immunosuppressive medications, periodontitis before KT has a significant effect on posttransplant outcomes. Pretransplant periodontitis may modulate the immune response early after KT and reduce the risk of acute rejection but may have long-term negative effects on graft and patient survival. In the future, prospective studies analyzing the effectiveness of treatment for periodontitis prior to KT can clearly define the role of periodontitis and update pre- and post-treatment treatment strategies.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors' contributions

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References

- Di Benedetto A, Gigante I, Colucci S, Grano M. Periodontal disease: linking the primary inflammation to bone loss. *Clin Dev Immunol* 2013;2013:503754.
- Engelbreton SP, Lalla E, Lamster IB. Periodontitis and systemic disease. *N Y State Dent J* 1999;65:30–32.
- Akar H, Akar GC, Carrero JJ, Stenvinkel P, Lindholm B. Systemic consequences of poor oral health in chronic kidney disease patients. *Clin J Am Soc Nephrol* 2011;6:218–226.
- Sharma P, Dietrich T, Ferro CJ, Cockwell P, Chapple IL. Association between periodontitis and mortality in stages 3-5 chronic kidney disease: NHANES III and linked mortality study. *J Clin Periodontol* 2016;43:104–113.
- Zhang J, Jiang H, Sun M, Chen J. Association between periodontal disease and mortality in people with CKD: a meta-analysis of cohort studies. *BMC Nephrol* 2017;18:269.
- Han SS, Shin N, Lee SM, Lee H, Kim DK, Kim YS. Correlation between periodontitis and chronic kidney disease in Korean adults. *Kidney Res Clin Pract* 2013;32:164–170.
- Kitamura M, Mochizuki Y, Miyata Y, et al. Pathological characteristics of periodontal disease in patients with chronic kidney disease and kidney transplantation. *Int J Mol Sci* 2019;20:3413.
- Kim J, Amar S. Periodontal disease and systemic conditions: a bidirectional relationship. *Odontology* 2006;94:10–21.
- Milone MT, Kamath AF, Israelite CL. Converting between high- and low-sensitivity C-reactive protein in the assessment of peri-prosthetic joint infection. *J Arthroplasty* 2014;29:685–689.
- Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. *J Periodontol* 2018;89 Suppl 1:S159–S172.
- Falcao A, Bullón P. A review of the influence of periodontal treatment in systemic diseases. *Periodontol* 2000 2019;79:117–128.
- Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat Rev Immunol* 2015;15:30–44.
- Nagpal R, Yamashiro Y, Izumi Y. The two-way association of periodontal infection with systemic disorders: an overview. *Mediators Inflamm* 2015;2015:793898.
- Ricardo AC, Athavale A, Chen J, et al. Periodontal disease, chronic kidney disease and mortality: results from the third National Health and Nutrition Examination Survey. *BMC Nephrol* 2015;16:97.
- Kshirsagar AV, Grubbs V. Periodontal disease and CKD-associated morbidity: is there now enough evidence to move from observation to intervention? *Am J Kidney Dis* 2015;66:181–3.
- Gowdak LH, Santos-Paul MA, Neves RS, et al. Treatment of periodontal disease significantly affects the rate of cardiovascular events in patients with chronic kidney disease. *J Am Coll Cardiol* 2019;73(9S1):168.
- Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* 2018;15:505–522.
- Shaqman MH. Periodontitis, inflammatory markers and solid organ transplant recipients [master's these]. Storrs (CT): University of Connecticut; 2009.
- Tsukamoto H, Clise-Dwyer K, Huston GE, et al. Age-associated increase in lifespan of naive CD4 T cells contributes to T-cell homeostasis but facilitates development of functional defects. *Proc*

- Natl Acad Sci U S A* 2009;106:18333–18338.
20. Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008;3:1526–1533.
 21. Okui T, Aoki-Nonaka Y, Nakajima T, Yamazaki K. The role of distinct T cell subsets in periodontitis: studies from humans and rodent models. *Curr Oral Health Rep* 2014;1:114–123.
 22. Steffens JP, Masi S, D’Aiuto F, Spolidorio LC. Telomere length and its relationship with chronic diseases: new perspectives for periodontal research. *Arch Oral Biol* 2013;58:111–117.
 23. Masi S, Salpea KD, Li K, et al. Oxidative stress, chronic inflammation, and telomere length in patients with periodontitis. *Free Radic Biol Med* 2011;50:730–735.
 24. Ioannidou E, Shaqman M, Burlison J, Dongari-Bagtzoglou A. Periodontitis case definition affects the association with renal function in kidney transplant recipients. *Oral Dis* 2010;16:636–642.
 25. Boratyńska M, Radwan-Oczko M, Falkiewicz K, Klinger M, Szyber P. Gingival overgrowth in kidney transplant recipients treated with cyclosporine and its relationship with chronic graft nephropathy. *Transplant Proc* 2003;35:2238–2240.
 26. Koo EH, Jang HR, Lee JE, et al. The impact of early and late acute rejection on graft survival in renal transplantation. *Kidney Res Clin Pract* 2015;34:160–164.
 27. Randhawa P. T-cell-mediated rejection of the kidney in the era of donor-specific antibodies: diagnostic challenges and clinical significance. *Curr Opin Organ Transplant* 2015;20:325–332.
 28. Shirali AC, Bia MJ. Management of cardiovascular disease in renal transplant recipients. *Clin J Am Soc Nephrol* 2008;3:491–504.
 29. Genctoy G, Ozbek M, Avcu N, et al. Gingival health status in renal transplant recipients: relationship between systemic inflammation and atherosclerosis. *Int J Clin Pract* 2007;61:577–582.
 30. Wynnimko M, Walicka M, Sanchak Y, et al. Influence of chronic periodontitis on the long-term mortality and cardiovascular events in kidney transplant recipients. *J Clin Med* 2020;9:1968.
 31. Ravidà A, Qazi M, Troiano G, et al. Using periodontal staging and grading system as a prognostic factor for future tooth loss: a long-term retrospective study. *J Periodontol* 2020;91:454–461.
 32. Kornman KS, Papapanou PN. Clinical application of the new classification of periodontal diseases: ground rules, clarifications and “gray zones”. *J Periodontol* 2020;91:352–360.
 33. Hienz SA, Paliwal S, Ivanovski S. Mechanisms of bone resorption in periodontitis. *J Immunol Res* 2015;2015:615486.