Published in final edited form as:

Oral Dis. 2010 October ; 16(7): 636–642. doi:10.1111/j.1601-0825.2010.01665.x.

Periodontitis case definition affects the association with renal function in kidney transplant recipients

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Abstract

Aim—The aim of this analysis is to investigate the association between periodontal status and renal allograft function in a cohort of renal transplant patients using different periodontitis case definitions.

Material & Methods—58 kidney transplant patients were included. The subjects were classified into two groups, deterioration or stable/improvement of renal allograft function as expressed by the difference in glomerular filtration rate (GFR) between two time points at least 6 months apart. Chronic periodontitis was defined as: 1) two or more interproximal sites with CAL $\geq$ 4mm or two or more interproximal sites with PD $\geq$ 5mm (DEF1); 2) PD $\geq$ 5 or CAL $\geq$ 4 in at least 6 proximal sites (DEF2); and 3) PD $\geq$ 5 or CAL $\geq$ 4 in at least 2 proximal sites in each quadrant (DEF3).

Results—In a multivariate linear regression model, none of the continuous periodontal variables were significantly associated with deterioration of allograft function. Of the three definitions of chronic periodontitis only DEF2 emerged as significantly more prevalent in subjects with GFR deterioration and was a statistically significant predictor of GFR deterioration over time.

Conclusion—These findings underscore the importance of periodontitis “case definition” in the observed statistical associations between periodontitis and systemic disease.

Keywords

Chronic periodontitis; renal function; kidney transplant; glomerular filtration rate; periodontitis case definition; organ rejection

INTRODUCTION

More than 16,500 kidney transplants are performed across the US annually (2007 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1997-2006, Health Resources and Services Administration). Despite greatly improved 1-year survival rates of renal transplants from living and deceased donors ($\approx$ 90-95%), the 10-year graft survival rates fall dramatically to 46-58% (Cecka, 2005). In renal transplants, 50–80% of these late failures are

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attributable to chronic allograft nephropathy (CAN) (Matas et al., 2001, Cecka, 2005) which is considered the most important cause of renal graft failure after the first year of transplantation (Dennis et al., 1989, Matas et al., 2001). CAN is a descriptive term for a number of histologic lesions in renal transplants characterized by progressive interstitial fibrosis, glomerulopathy, mesangial matrix increase, vascular fibrous intimal thickening and arteriolar hyaline thickening (Yates & Nicholson, 2006). Clinically, CAN presents as progressive deterioration in renal function (reduced glomerular filtration rate), proteinuria, and occasionally, de novo or secondary hypertension.

Several alloimmune-dependent factors (e.g. acute rejection episodes, HLA mismatching) and alloimmune-independent factors (e.g. graft ischemia, brain death, obesity) are believed to influence renal graft function (Yates & Nicholson, 2006). Interestingly, a heightened pre-transplant or post-transplant systemic inflammation, as measured by a multitude of serum inflammation markers (e.g. C-reactive protein (CRP), vascular adhesion molecule-1, interleukin 12) has been associated with worse renal allograft outcomes (Perez et al., 2000, Perez et al., 2003, van Ree et al., 2007, Fink et al., 2002, Berber et al., 2008). Thus, it appears that elevated systemic inflammation sets the stage for an accentuated inflammatory response to the allograft and deterioration of graft function.

Systemic inflammation has been linked to periodontal inflammation. There is accumulating evidence that links periodontal disease to various systemic conditions, including cardiovascular disease (Bahekar et al., 2007), stroke (Desvarieux et al., 2003), diabetes mellitus (Taylor et al., 1996, Lamster & Lalla, 2001), poor pregnancy outcomes (Riche et al., 2002, Ruma et al., 2008, Canakci et al., 2007) and end-stage renal disease (Kshirsagar et al., 2009). One of the proposed mechanisms for this association is that these diseases share a common, genetically-determined, susceptible phenotype whereby periodontitis and systemic disease are not causally related but both manifest in an individual with a hyper-inflammatory phenotype (Seymour et al., 2007). Several studies have shown a hyper-active phagocytic cell phenotype in chronic periodontitis patients (Matthews et al., 2007, Fredriksson et al., 2003), in which excessive production of inflammatory cytokines, proteases and reactive oxygen radicals result in destruction of periodontal tissues (Fredriksson et al., 2003, Matthews et al., 2007). Moreover, higher systemic inflammatory cytokine levels have been associated with periodontal disease (Paraskevas et al., 2008, Takahashi et al., 1994, Noack et al., 2001, Tonetti et al., 2007, Ioannidou et al., 2006). The latter observations also led to the hypothesis that periodontal inflammation may contribute incrementally to systemic inflammatory mediator levels and thereby amplify systemic disease processes (Dave & Van Dyke, 2008, Seymour et al., 2007).

Given the evidence that links periodontitis to a hyper-inflammatory phenotype (Fredriksson et al., 2003, Matthews et al., 2007) and higher systemic inflammatory cytokine levels in transplant (Ioannidou et al., 2006) and other patient populations (Paraskevas et al., 2008, Nankivell et al., 2004, Noack et al., 2001), we hypothesized that periodontal disease could serve as a marker to identify subjects with a systemic hyper-inflammatory phenotype that may be at greater risk for long-term renal allograft deterioration. The aim of this analysis is to investigate the association between the periodontal status of a cohort of renal transplant patients and renal allograft function.

MATERIALS & METHODS

Subject recruitment

The study that followed a cross-sectional single cohort design was approved by the University of Connecticut Health Center and Hartford Hospital Institutional Review Boards (IRB). The population under investigation was a subset of subjects from a larger

investigation that included 90 renal and cardiac transplant patients. Renal transplant recipients were screened during routine outpatient visits at Hartford Hospital Transplant Center. Inclusion criteria were: 1) at least 1 year post-transplant; 2) negative history of antibiotic use during the preceding 4 months; 3) no periodontal treatment within the last year; and 4) availability of at least two serum creatinine values 6 months apart and at least 6 months after the transplant. Fifty-eight renal transplant patients who met these criteria and signed the IRB approved informed consent forms were included.

Data Collection

Medical information of the subjects was extracted from medical records. A standardized extraction form was used. The extracted data included: patient demographics (age, gender, ethnicity, weight, and height), co-existing systemic conditions e.g. diabetes (yes/no), smoking status (current, former and never smoker), number of years post-transplant, history of rejection episodes, medication regimen and dosage, graft rejection risk factors (e.g. human leukocyte antigen (HLA) mismatching, panel reactive antibody (PRA) score, cadaveric or living donor, related or unrelated donor), creatinine clearance laboratory results and history of graft biopsy.

Using two serum creatinine values per subject as described in the inclusion criteria, two glomerular filtration rate (GFR) values (one at each time point) were calculated using the 4-variable simplified Modification of Diet in Renal Disease (MDRD) formula (estimated $GFR = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.210 \text{ if Black}] \times [0.742 \text{ if Female}]$) (Levey et al., 2006). Accordingly, the determination of renal allograft function over time was based on the difference:

$$\Delta GFR = GFR(\text{time1}) - GFR(\text{time2})$$

When $\Delta GFR > 0$, the subject was included in the deterioration group. Conversely, when $\Delta GFR \leq 0$, the subject was included in the stable/improvement group.

Periodontal Examination

Subjects received a full mouth periodontal examination at six sites per tooth. Four periodontists, that were calibrated prior to the initiation of the study, performed the exam using a Michigan O probe with Williams markings. The following parameters were evaluated and recorded: missing teeth (excluding third molars), plaque score (PS), bleeding on probing (BOP), probing depth (PD), clinical attachment level (CAL) and gingival overgrowth (GO) based on the gingival overgrowth index by Pernu et al. (Pernu et al., 1992). Chronic periodontitis was defined using 3 different definitions: the first definition (DEF1) was the CDC/AAP working definition of moderate periodontitis. Accordingly, chronic periodontitis was defined as two or more interproximal sites with $CAL \geq 4\text{mm}$ (not on the same tooth) or two or more interproximal sites with $PD \geq 5\text{mm}$ (not on the same tooth). The second definition of chronic periodontitis (DEF2) was $PD \geq 5$ or $CAL \geq 4$ in at least 6 proximal sites. The third definition of chronic periodontitis (DEF3) was $PD \geq 5$ or $CAL \geq 4$ in at least 2 proximal sites in each quadrant. Both DEF2 and DEF3 were arbitrary definitions with clinical cutoff thresholds representing an escalating extent of periodontal destruction compared to DEF1 (CDC/AAP definition).

Statistical Analyses

A natural log transformation was applied to non-normally distributed variables. Means and medians were calculated for continuous variables. Student t-test (for continuous variables) and chi-square or Fisher's exact test (for categorical variables) were used to test for

differences between the groups (GFR deterioration vs. stable/improvement). A multivariate, repeated measures, linear regression analysis was applied to determine significant predictors of the within-subject change in GFR values over time. Variables that turned a p value >0.2 were excluded from the final regression model. A p value ≤ 0.05 was considered statistically significant. When $0.05 < p < 0.1$, we considered differences to have a trend to significance (Sterne and Smith, 2001).

RESULTS

The population demographic and medical data are reported in Tables 1 and 2, respectively. Diabetic patients comprised 52% of the subjects. There were no current smokers in this population. The median number of years post-transplant was more than 7 years. Approximately, 60% of the subjects had a deterioration of GFR levels (mean $\Delta\text{GFR}=56$ ml/min/1.73 m²), whereas 40% of the subjects had an improvement of GFR levels (mean $\Delta\text{GFR}=-44$ ml/min/1.73 m²). Additional descriptive statistics on GFR values in the two groups appear in Table 3. Prevalence of chronic periodontitis according to case definition appears in Table 4, whereas specific periodontal parameters in the GFR stable/improvement vs. deterioration groups are reported in Table 5. Although the prevalence of periodontitis was higher in the GFR deterioration group regardless of the case definition used, the difference was statistically significant only with DEF2 (χ^2 (1, $n=53$), $p=0.04$, $\phi=0.28$) (Table 4). There were no statistically significant differences in mean: PD, CAL, percentage of sites with BOP, plaque score, percentage of sites with $\text{PD} \geq 5\text{mm}$, percentage of sites with $\text{CAL} \geq 4\text{mm}$ or the number of missing teeth among the two groups (Table 5).

A multivariate, repeated measures, linear regression analysis was conducted to determine significant predictors of the within-subject GFR change over time (Table 6). The variables included were race, body-mass index (BMI), diabetes status (yes/no), smoking history (former/never), living or cadaveric donor, hypertension, dialysis before transplantation, cold ischemic time, delayed graft function, acute rejection episodes (yes/no), panel reactive antibody score, HLA mismatch (less than 5 vs. 5 mismatches or more, prednisone use (yes/no), cyclosporine use (yes/no). Continuous periodontal parameters (mean PD, mean CAL, percentage of sites with BOP, percentage of sites with $\text{PD} \geq 5\text{mm}$, percentage of sites with $\text{CAL} \geq 4\text{mm}$) and the number of missing teeth were included individually in the model (i.e. they were not tested simultaneously). Chronic Periodontitis, as defined by each definition was included in the model individually. Variables that returned a p value >0.2 were excluded from the final model. Accordingly, the following variables were excluded from the final analysis: gender, race, BMI, diabetes status (yes/no), smoking history (former/never), living or cadaveric donor, dialysis before transplantation, cold ischemic time, delayed graft function, panel reactive antibody score, HLA mismatch (less than 5 vs. 5 mismatches or more), prednisone use (yes/no), cyclosporine use (yes/no). History of acute rejection ($p=0.03$), having a deceased donor ($p=0.01$), and being hypertensive ($p=0.05$) statistically significantly predicted deterioration of renal allograft function. When the continuous periodontal variables were introduced individually into the model, higher percentage of sites with BOP and higher mean PD showed a trend towards statistical significance in predicting deterioration of allograft function (percentage sites with BOP: $F=3.27$, $p=0.08$; mean PD: $F=3.02$, $p=0.09$). Other continuous periodontal variables were not statistically significant in the model (percentage of sites with $\text{PD} \geq 5\text{mm}$: $F=2.28$, $p=0.14$; mean CAL: $F=0.06$, $p=0.81$, percentage of sites with $\text{CAL} \geq 4\text{mm}$: $F=0.74$, $p=0.39$; number of missing teeth: $F=0.15$, $p=0.70$). Chronic Periodontitis as defined by DEF2 emerged as a statistically significant predictor of GFR deterioration over time. In contrast, chronic periodontitis according to DEF1 or DEF3 was not significant a predictor (Table 6).

DISCUSSION

The success that has been achieved in improving early survival rates of renal transplants is still over-shadowed by a significant drop in long-term patient and graft survival after 10 years (Meier-Kriesche et al., 2004). Several parameters have been shown to be correlated with long-term allograft outcomes such as acute rejection episodes (Matas et al., 1994), the number of human leukocyte antigen (HLA) mismatches (McKenna et al., 1998), delayed graft function (Shoskes & Cecka, 1997), and having a living vs. a cadaveric donor (Massy et al., 1996). Nevertheless, these parameters can't explain the variation in the clinical course and outcome of organ transplantation.

In this work we hypothesized that periodontal disease is one marker of a systemic hyper-inflammatory phenotype and if present in renal transplant recipients, it might indicate a greater risk for long-term renal allograft deterioration. Although this hypothesis does not necessarily suggest causality, this association would have several implications in this patient population. For example, a history of periodontitis would identify a population in need of more strict criteria in HLA-matching before transplantation. This could also necessitate closer monitoring of periodontitis-susceptible individuals after renal transplantation for signs of CAN and additional graft surveillance biopsies might be indicated. Conventionally, graft failure is suspected only when a continued and irreversible reduction of renal function has become clinically apparent, as a combination of hypertension and proteinuria, which prompts renal allograft biopsies when it may already be too late (Morath et al., 2003).

This analysis was performed on a subset of the renal allograft recipients from a larger renal and cardiac transplant recipient population. One of the inclusion criteria was the availability of two serum creatinine lab results that were taken at least 6 months after the transplantation and were at least 6 months apart. Those cutoff points were chosen since one large study showed that allograft function at 6 months post-transplant, as measured by creatinine values, and the changes that occurred 6 months later were related to the 5-year survival of the graft (Hariharan et al., 2002). In our study, the GFR values were estimated using the simplified MDRD formula. The simplified MDRD formula showed comparable accuracy and correlation to other MDRD formulas in estimating GFR in renal transplant recipients, and better prediction of true GFR compared to the Cockcroft & Gault formula (Cockcroft & Gault, 1976, Poge et al., 2005). The mean Δ GFR values in our population and frequency of improvement/deterioration over time are in agreement with longitudinal observations of similar populations in other studies (Wigger et al., 2001, Gera et al., 2007). Importantly, all subjects with a history of renal biopsy were found to be in the deterioration group, which is expected since renal biopsy is indicated when renal function is reduced (Morath et al., 2003).

Traditionally, investigators have used arbitrary definitions of chronic periodontitis in epidemiologic studies assessing the relationship with systemic diseases (de Pablo et al., 2008, M.S. Tonetti, 2005, Manau et al., 2008). In this analysis, periodontal destruction was measured using a series of continuous variables and 3 different "disease case" definitions. The decision to include more than one case definition was triggered by a recent study which showed that when different disease definitions were applied in the same patient population, considerably different associations were found between periodontitis and systemic diseases (Manau et al., 2008). In agreement with this study we found that only one of the 3 case definitions provided statistically significant results in a multivariate regression model. Other medical variables (history of rejection, cadaveric donor and hypertension) found to be significant are in agreement with previous studies (Matas et al., 2001, Nickerson et al., 1998, Matas et al., 1994). Although an association between periodontitis, human cytomegalovirus

(HCMV) infection and renal transplant complications has been found (Nowzari et al., 2003), we were unable to confirm this due to missing HCMV data in our population.

Continuous periodontal variables were not significantly different between the GFR groups. However, clinically small trends were observed for greater periodontal destruction in the GFR deterioration group. In addition, using all definitions, chronic periodontitis showed higher prevalence in the GFR deterioration group compared to the GFR improvement group. These findings suggest that periodontal destruction might be a risk indicator for renal allograft deterioration. Furthermore, when continuous periodontal variables were tested in the multivariate regression model, there was a suggestion that the extent and severity of periodontal destruction, as expressed by percentage of sites with BOP and/or mean PD, could predict GFR deterioration. Thus the “periodontitis” case definitions tested in this study attempted to capture an escalating severity of the disease, from DEF1 (lowest) to DEF3 (highest severity). Surprisingly, only the case definition representing a “medium size” disease severity (DEF2) showed statistically significant findings. This finding would argue against a strictly linear relationship between disease severity and the observed associations. However, the cutoff points used in DEF2 were more strict in defining disease severity compared to other clinical studies that used definitions with either fewer periodontally involved sites (Bassani et al. 2007, Holbrook et al. 2004, Jarjoura et al. 2005, Jeffcoat et al. 2001) or lower PD or CAL cutoff points (Goepfert et al. 2004, Holbrook et al. 2004, Jarjoura et al. 2005, Jeffcoat et al. 2001).

Our “a priori” power analysis to investigate differences in the prevalence of chronic periodontitis in kidney or heart transplant subjects compared to systemically healthy controls, revealed the need for a minimum of 54 subjects, for a power of 80% and alpha-value of 0.05. In this subgroup analysis of 58 kidney transplant subjects, we applied three different definitions that had not been considered in our “a priori” power calculations. Post-hoc power calculations revealed that in order to attain this level of power for each case definition in a multivariate regression model with 4 predictors (as shown in Table 6) we needed a minimum of 96 subjects for DEF 1, 48 subjects for DEF2, and 71 subjects for DEF3. This may raise the question whether an adequate number of subjects was available for statistically significant comparisons using DEF1 or DEF3. However, although such post-hoc power analyses are tempting, they are not conclusive and often lead to misinterpretation of the results. For example even for a study with a priori sufficient power, if the results are negative, the post hoc power analysis based on the observed results will always show that the study was underpowered (Levine, 2001, Freedman, 1999).

An important limitation of our analysis was that the most recent serum creatinine test was not performed at the time of the oral examination but was retrieved from the medical record. However, the major focus of this investigation was to test the effect of case definition selection on the observed associations between renal function and periodontitis within a kidney transplant population. Moreover, the findings of this study could contribute to power estimates of future longitudinal studies with prospective monitoring of allograft function, periodontal status and protocol biopsies in a larger population that will provide definitive conclusions on the association between periodontitis and renal function in this and other populations.

In conclusion, our findings suggest that chronic periodontitis is more prevalent in the GFR deterioration group and may be a predictor for GFR deterioration over time. However, the impact of the disease thresholds that were used to define a “periodontitis case” was also evident in these associations. These findings underscore the importance of the “case definition of periodontitis” selection in studies investigating the link between periodontitis

and systemic diseases. Based on these findings we propose that future studies in this field use more than one case definitions to strengthen the validity of the observed associations.

Acknowledgments

This study was supported by NIH/NIDCR Research grants R21DE16466 awarded to AD-B and K23DE018689 awarded to EI. This research was also supported in part by a General Clinical Research Center grant from NIH (M01RR06192) awarded to UCHC. Special thanks to Dr. David Hull, Head of the Transplant Unit – Hartford Hospital, for his contribution.

Conflict of Interest: This study was supported by the National Institute of Health, National Institute of Dental and Craniofacial Research grants awarded to ADB (R21DE16466) and to EI (K23DE018689). This research was also supported in part by a General Clinical Research Center grant from NIH (M01RR06192) awarded to UCHC.

REFERENCES

- 2007 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1997-2006. Health Resources and Services Administration HS;
- Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *Am Heart J.* 2007; 154:830–7. [PubMed: 17967586]
- Berber I, Yigit B, Isitmangil G, Tellioglu G, Ozgezer T, Gulle S, Turkmen F, Titiz I. Evaluation of pretransplant serum cytokine levels in renal transplant recipients. *Transplant Proc.* 2008; 40:92–3. [PubMed: 18261555]
- Canakci V, Canakci CF, Yildirim A, Incec M, Eltas A, Erturk A. Periodontal disease increases the risk of severe pre-eclampsia among pregnant women. *J Clin Periodontol.* 2007; 34:639–45. [PubMed: 17590155]
- Cecka JM. The OPTN/UNOS Renal Transplant Registry. *Clin Transpl.* 2005;1–16. [PubMed: 17424721]
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31–41. [PubMed: 1244564]
- Dave S, Van Dyke T. The link between periodontal disease and cardiovascular disease is probably inflammation. *Oral Dis.* 2008; 14:95–101. [PubMed: 18302669]
- de Pablo P, Dietrich T, McAlindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. *J Rheumatol.* 2008; 35:70–6. [PubMed: 18050377]
- Dennis MJ, Foster MC, Ryan JJ, Burden RP, Morgan AG, Blamey RW. The increasing importance of chronic rejection as a cause of renal allograft failure. *Transpl Int.* 1989; 2:214–7. [PubMed: 2697211]
- Desvarieux M, Demmer RT, Rundek T, Boden-Albala B, Jacobs DR Jr. Papapanou PN, Sacco RL. Relationship Between Periodontal Disease, Tooth Loss, and Carotid Artery Plaque: The Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Stroke.* 2003; 34:2120–2125. [PubMed: 12893951]
- Fink JC, Onuigbo MA, Blahut SA, Christenson RH, Mann D, Bartlett ST, Weir MR. Pretransplant serum C-reactive protein and the risk of chronic allograft nephropathy in renal transplant recipients: a pilot case-control study. *Am J Kidney Dis.* 2002; 39:1096–101. [PubMed: 11979355]
- Fredriksson MI, Gustafsson AK, Bergstrom KG, Asman BE. Constitutionally hyperreactive neutrophils in periodontitis. *J Periodontol.* 2003; 74:219–24. [PubMed: 12666711]
- Freedman KB, Bernstein J. Sample size and statistical power in clinical orthopaedic surgery. *J Bone Joint Surg.* 2001; 81:1454–140.
- Gera M, Slezak JM, Rule AD, Larson TS, Stegall MD, Cosio FG. Assessment of changes in kidney allograft function using creatinine-based estimates of glomerular filtration rate. *Am J Transplant.* 2007; 7:880–7. [PubMed: 17391131]

- Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int.* 2002; 62:311–8. [PubMed: 12081593]
- Ioannidou E, Malekzadeh T, Dongari-Bagtzoglou A. Effect of periodontal treatment on serum C-reactive protein levels: a systematic review and meta-analysis. *J Periodontol.* 2006; 77:1635–42. [PubMed: 17032104]
- Kshirsagar AV, Craig RG, Moss KL, Beck JD, Offenbacher S, Kotanko P, Klemmer PJ, Yoshino M, Levin NW, Yip JK, Almas K, Lupovici EM, Usvyat LA, Falk RJ. Periodontal disease adversely affects the survival of patients with end-stage renal disease. *Kidney Int.* 2009; 75:746–51. [PubMed: 19165177]
- Lamster IB, Lalla E. Periodontal disease and diabetes mellitus: discussion, conclusions, and recommendations. *Ann Periodontol.* 2001; 6:146–9. [PubMed: 11887457]
- Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006; 145:247–54. [PubMed: 16908915]
- Levine M, Ensom M. Post hoc power analysis: An idea whose time has passed? *Pharmacotherapy.* 2001; 21:405–409.
- M.S. Tonetti NC. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. *Journal of Clinical Periodontology.* 2005; 32:210–213. [PubMed: 16128839]
- Manau C, Echeverria A, Agueda A, Guerrero A, Echeverria JJ. Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. *J Clin Periodontol.* 2008; 35:385–97. [PubMed: 18341599]
- Massy ZA, Guijarro C, Wiederkehr MR, Ma JZ, Kasiske BL. Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. *Kidney Int.* 1996; 49:518–24. [PubMed: 8821839]
- Matas AJ, Gillingham KJ, Payne WD, Najarian JS. The impact of an acute rejection episode on long-term renal allograft survival (t1/2). *Transplantation.* 1994; 57:857–9. [PubMed: 8154032]
- Matas AJ, Payne WD, Sutherland DE, Humar A, Gruessner RW, Kandaswamy R, Dunn DL, Gillingham KJ, Najarian JS. 2,500 living donor kidney transplants: a single-center experience. *Ann Surg.* 2001; 234:149–64. [PubMed: 11505060]
- Matthews JB, Wright HJ, Roberts A, Ling-Mountford N, Cooper PR, Chapple IL. Neutrophil hyper-responsiveness in periodontitis. *J Dent Res.* 2007; 86:718–22. [PubMed: 17652198]
- McKenna RM, Lee KR, Gough JC, Jeffery JR, Grimm PC, Rush DN, Nickerson P. Matching for private or public HLA epitopes reduces acute rejection episodes and improves two-year renal allograft function. *Transplantation.* 1998; 66:38–43. [PubMed: 9679819]
- Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant.* 2004; 4:378–83. [PubMed: 14961990]
- Morath C, Ritz E, Zeier M. Protocol biopsy: what is the rationale and what is the evidence? *Nephrol. Dial. Transplant.* 2003; 18:644–647. [PubMed: 12637628]
- Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Chapman JR, Allen RD. Calcineurin inhibitor nephrotoxicity: longitudinal assessment by protocol histology. *Transplantation.* 2004; 78:557–65. [PubMed: 15446315]
- Nickerson P, Jeffery J, Gough J, McKenna R, Grimm P, Cheang M, Rush D. Identification of clinical and histopathologic risk factors for diminished renal function 2 years posttransplant. *J Am Soc Nephrol.* 1998; 9:482–7. [PubMed: 9513912]
- Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol.* 2001; 72:1221–7. [PubMed: 11577954]
- Nowzari H, Jorgensen MG, Aswad S, Khan N, Osorio E, Safarian A, Shidban H, Munroe S. Human cytomegalovirus-associated periodontitis in renal transplant patients. *Transplant Proc.* 2003; 35:2949–52. [PubMed: 14697947]
- Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. *J Clin Periodontol.* 2008; 35:277–90. [PubMed: 18294231]

- Perez RV, Brown DJ, Katznelson SA, Dubin JA, Muller HG, Chang T, Rudich SM, McVicar JP, Kaysen GA. Pretransplant systemic inflammation and acute rejection after renal transplantation. *Transplantation*. 2000; 69:869–74. [PubMed: 10755542]
- Perez RV, Huang CQ, Johnson JR, Galloway BJ, Gandhi MM, McVicar JP, Troppmann C. Pretransplantation soluble adhesion molecule expression predicts outcome after living donor renal transplantation. *Arch Surg*. 2003; 138:1113–9. discussion 1119-20. [PubMed: 14557129]
- Pernu HE, Pernu LM, Huttunen KR, Nieminen PA, Knuuttila ML. Gingival overgrowth among renal transplant recipients related to immunosuppressive medication and possible local background factors. *J Periodontol*. 1992; 63:548–53. [PubMed: 1625155]
- Poge U, Gerhardt T, Palmedo H, Klehr HU, Sauerbruch T, Woitas RP. MDRD equations for estimation of GFR in renal transplant recipients. *Am J Transplant*. 2005; 5:1306–11. [PubMed: 15888034]
- Riche EL, Boggess KA, Lief S, Murtha AP, Auten RL, Beck JD, Offenbacher S. Periodontal disease increases the risk of preterm delivery among preeclamptic women. *Ann Periodontol*. 2002; 7:95–101. [PubMed: 16013222]
- Ruma M, Boggess K, Moss K, Jared H, Murtha A, Beck J, Offenbacher S. Maternal periodontal disease, systemic inflammation, and risk for preeclampsia. *Am J Obstet Gynecol*. 2008; 198(389):e1–5. [PubMed: 18295179]
- Seymour GJ, Ford PJ, Cullinan MP, Leishman S, Yamazaki K. Relationship between periodontal infections and systemic disease. *Clin Microbiol Infect*. 2007; 13(Suppl 4):3–10. [PubMed: 17716290]
- Shoskes DA, Cecka JM. Effect of delayed graft function on short- and long-term kidney graft survival. *Clin Transpl*. 1997:297–303. [PubMed: 9919413]
- Sterne J, Smith GD. Sifting the evidence-what's wrong with significance tests? *BMJ*. 2001; 322:226–230. [PubMed: 11159626]
- Takahashi K, Takashiba S, Nagai A, Takigawa M, Myoukai F, Kurihara H, Murayama Y. Assessment of interleukin-6 in the pathogenesis of periodontal disease. *J Periodontol*. 1994; 65:147–53. [PubMed: 8158511]
- Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol*. 1996; 67:1085–93. [PubMed: 8910827]
- Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. *N Engl J Med*. 2007; 356:911–20. [PubMed: 17329698]
- van Ree RM, Oterdoom LH, de Vries AP, Gansevoort RT, van der Heide JJ, van Son WJ, Ploeg RJ, de Jong PE, Gans RO, Bakker SJ. Elevated levels of C-reactive protein independently predict accelerated deterioration of graft function in renal transplant recipients. *Nephrol Dial Transplant*. 2007; 22:246–53. [PubMed: 16998222]
- Wigger M, Druckler E, Muscheites J, Stolpe HJ. Course of glomerular filtration rate after renal transplantation and the influence of hypertension. *Clin Nephrol*. 2001; 56:S30–4. [PubMed: 11770810]
- Yates PJ, Nicholson ML. The aetiology and pathogenesis of chronic allograft nephropathy. *Transpl Immunol*. 2006; 16:148–57. [PubMed: 17138047]

Table 1

Demographic Characteristics

Variable	Mean $\pm$ SD, (Median)
Age	52.8 $\pm$ 12.0, (53.3)
Gender (female) (%)	41
Race (black) (%)	24

Table 2

Medical characteristics

Variable	Mean, Median (Quartiles)
Diabetics (%)	52
Smoking (former) (%)	31
Yrs post-transplant	7.6±4.9, 7.1(3.8, 11.0)
History of acute rejection (%)	33
Pre-transplant dialysis (%)	78
Living donor (related or unrelated) (%)	43%
Ca++ channel blockers (%)	28
Cyclosporin (%)	38
Prednisone (%)	91
Mycophenolate (%)	72
Tacrolimus (%)	57
Azathioprine (%)	21
Sirolimus (%)	14

Table 3

Mean, median and quartiles of Δ GFR values in the deterioration and stable/improvement groups

Variable	Mean, Median (Quartiles)
Mean Δ GFR in deterioration group (mL/min/1.73 m ²)	56, 48 (66,36)
Mean Δ GFR in stable/improvement group (mL/min/1.73 m ²)	-44, -44 (-26, -56)

Table 4

Chronic periodontitis (CP) frequency (subject numbers and percentages) in each GFR group according to the three definitions.

Definition	GFR deterioration (%)	GFR stable/improvement (%)	Total in both GFR groups (%)	P value
DEF1	25 (71)	13 (57)	38 (65.5)	p=0.37* (NS)
DEF2	32 (91)	16 (70)	48 (82.8)	p= 0.04 *
DEF3	20 (57)	9 (39)	29 (50)	p=0.18 ** (NS)

* χ^2 test

** Fisher's exact test

Table 5

Continuous Periodontal Variables in the two GFR Groups

Variable	GFR deterioration		GFR improvement		P value*
	Mean±SD	Median (25 th , 75 th quartiles)	Mean±SD	Median (25 th , 75 th quartiles)	
Mean PD (mm)	2.8 ± 0.4	2.7 (2.4, 3.2)	2.6 ± 0.5	2.6 (2.4, 3.0)	0.25 (NS)
Mean CAL (mm)	3.0 ± 0.8	2.8 (2.5, 3.3)	2.9 ± 0.7	2.7 (2.4, 3.4)	0.72 (NS)
BOP (%)	18.8 ± 15.5	15.0 (6.5, 25.0)	14.7 ± 13.8	7.7 (4.6, 28.5)	0.14 (NS)
PS (%)	50.7 ± 29.0	53.6 (28.3, 76.9)	43.0 ± 33.0	42.4 (10.7, 74.4)	0.35 (NS)
Missing teeth	2.6 ± 2.6	2.0 (1.0, 4.0)	4.5 ± 4.5	4.0 (0.0, 8.0)	0.29 (NS)
Sites with CAL ≥ 4mm (%)	16.6 ± 20.1	9.1 (3.1, 19.2)	14.9 ± 19.8	3.0 (1.8, 20.8)	0.30 (NS)
Sites with PD ≥ 5mm (%)	7.0 ± 9.2	2.4 (0.0, 12.3)	5.6 ± 9.0	0.0 (0.0, 11.4)	0.22 (NS)

Table 6

Multivariate, repeated measures, linear regression models designed based on the three chronic periodontitis “case definitions”.

Model 1				
Variable	F	Sig.	β	Observed Power
History of acute rejection	7.02	0.01	0.36	0.57
Cadaveric donor	6.66	0.01	0.35	0.54
Hypertension	4.34	0.04	0.29	0.80
Chronic periodontitis (DEF1)	0.05	0.83	0.03	0.06

Model 2				
Variable	F	Sig.	β	Observed Power
History of acute rejection	5.14	0.03	0.31	0.60
Cadaveric donor	7.00	0.01	0.36	0.74
Hypertension	4.29	0.04	0.29	0.53
Chronic periodontitis (DEF2)	4.51	0.04	0.29	0.55

Model 3				
Variable	F	Sig.	β	Observed Power
History of acute rejection	4.79	0.03	0.30	0.57
Cadaveric donor	6.52	0.01	0.34	0.71
Hypertension	4.00	0.05	0.28	0.50
Chronic periodontitis (DEF3)	0.89	0.35	0.13	0.15