Periodontal and chronic kidney disease

**Periodontal and chronic kidney disease association: a systematic review and meta-analysis**

Kostas Kapellas¹*, Ankur Singh¹,², Maitê Bertotti³, Gustavo Nascimento⁴, Lisa M. Jamieson¹ on behalf of the Perio-CKD collaboration

1. Australian Research Centre for Population Oral Health, The University of Adelaide, South Australia, Australia
2. Melbourne School of Population and Global Health, The University of Melbourne, Australia
3. School of Dentistry, Universidade Federal do Rio Grande do Sul, Brazil
4. Department of Dentistry and Oral Health, Aarhus Universitet Institut for Odontologi, Aarhus, Denmark

**Corresponding author**

Kostas Kapellas: Australian Research Centre for Population Oral Health;
Adelaide Dental School
Level 9, 57 North Terrace, Adelaide South Australia 5005;
Tel: +618 8313 7339
Email: kostas.kapellas@adelaide.edu.au

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ABSTRACT

Aim: Chronic kidney disease (CKD) and kidney failure is increasing globally and evidence from observational studies suggest periodontal disease may contribute to kidney functional decline.

Methods: Electronic searches of the PubMed, EMBASE, Web of Science, Scopus and Cochrane Library databases were conducted for the purposes of conducting a systematic review. Hand searching of reference lists was also performed. Meta-analysis of observational studies involving periodontal disease and chronic kidney disease in adults was performed.

Results: A total of 17 studies were selected from an initial 4,055 abstracts. Pooled estimates indicated the odds of having CKD were 60% higher among patients with periodontitis: pooled OR 1.60 (95% CI 1.44 — 1.79, I² 35.2%, P=0.11) compared to those without. Conversely, a similar magnitude but non-significant higher odds of having periodontal disease was found among people with CKD 1.69 (95% CI: 0.84, 3.40, I²=89.8%, P<0.00) versus non-CKD. Meta-regression revealed study quality based on the Newcastle-Ottawa Scale and statistical adjustment for potential
confounders explained almost 35% of the heterogeneity in the studies investigating the association between CKD and periodontitis.

**Conclusions:** Moderate evidence for a positive association between periodontitis and CKD exists. Evidence for the opposite direction is extremely weak based on significant heterogeneity between studies.

**Keywords:** periodontal diseases; renal insufficiency, chronic; review, systematic; meta-analysis

**BACKGROUND**

Periodontitis is an inflammatory condition of the connective tissues around teeth. It is characterized by localized destruction of these tissues and, in severe cases, leads to tooth loss. This inflammation is caused by a unique set of bacteria which stimulate both innate and adaptive immune responses. Chronic kidney disease (CKD) for the present review is defined by the glomerular filtration rate (GFR) below 60mL/min/1.73m² for at least three months. End-Stage Kidney Disease (ESKD) is diagnosed when GFR is 15mL/min/1.73m² or below. Severe periodontitis was ranked as the 6th most prevalent condition among 291 conditions and CKD was ranked as the 13th leading cause of death in the Global Burden of Disease study.

Risk factors for CKD include increasing age, hypertension, sub-optimally managed diabetes, tobacco smoking, racial background, and systemic inflammation. Likewise, smoking, increasing age, and diabetes have been identified as risk factors for periodontal disease.
Proposed mechanisms connecting periodontitis with CKD may involve systemic inflammation. During active phases of periodontitis, locally produced inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α act systemically to raise C-reactive protein levels\textsuperscript{15,16} which may lead to the progression of CKD. An alternative theory suggests that periodontal bacteria (or their lipopolysacharides) enter the systemic circulation and exert their effects beyond the periodontium\textsuperscript{17,18}. If a causal relationship between periodontitis and CKD were proven, periodontal treatment may reduce the risk of CKD\textsuperscript{19}. Conversely, it is possible that CKD may mechanistically influence the onset and/or progression of periodontal disease, possibly mediated by diabetes and hypertension\textsuperscript{20}.

The association between periodontal disease and CKD is presently unclear making it necessary to systematically assess the literature to verify if an association exists. Therefore, the purpose of this review is to evaluate existing evidence from published literature to determine, whether: 1) periodontitis is a risk factor for CKD, and 2) CKD is a risk factor for periodontitis.

**METHODS**

The protocol for this systematic review was registered with the International Prospective Register for Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/), registration number CRD42016033770. The MOOSE guidelines\textsuperscript{21} were used as the preparatory framework for this review.

**PICO**
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This review will attempt to answer two questions:

1) Are people with periodontal disease compared to those without periodontal disease more likely to have CKD?

**Population:** Adults with clinically-determined periodontal disease, **Intervention:** none, **Comparator:** Adults without clinically-determined periodontal disease, **Outcome:** Chronic kidney disease determined by GFR below 60mL/min/1.73m².

2) Are people with CKD compared to those without CKD more likely to have periodontal disease?

**Population:** Chronic kidney disease determined by GFR below 60mL/min/1.73m², **Intervention:** none, **Comparator:** Adults with GFR ≥ 60mL/min/1.73m², **Outcome:** adults with clinically-determined periodontal disease.

**Study designs included in this review**

Cross-sectional, case-control and cohort studies were included if the association with periodontitis was examined in CKD patients, or if the presence of CKD was examined in periodontitis patients. Additionally, baseline data from any interventional studies that met the inclusion criteria were extracted and included in the meta-analysis.

**Type of participants and inclusion criteria**

Studies were included if they measured periodontal status via clinical oral assessments of periodontal pocket depth (PPD) and/or clinical attachment level (CAL) while studies solely reliant on using radiographic or visual criteria to determine periodontal status were excluded. For CKD, studies were included when GFR was calculated or assessed to be at Stage 1 or worse.

**Excluded studies**
Case reports, literature reviews, commentaries and editorials were not included in this review. Additionally, studies in languages other than English were excluded.

Search Strategy & Sources

Electronic searches of PubMed, EMBASE, Web of Science, Scopus and Cochrane Library databases were conducted. Searches for eligible studies in this review were performed in duplicate by two authors both of whom are dental clinicians (KK and MB) with the aid of a university research librarian according to search criteria presented in Supplement Table 2.

All databases were searched up to and including 31st March 2017. Reference lists of previous reviews and of selected full-text articles were manually searched for additional articles. Both reviewers (KK and MB) independently screened the titles and abstracts and if found to be relevant, the full text of each article was evaluated for final inclusion. Disagreement between reviewers was resolved via discussion. Guidelines to engage a third reviewer in the event of unresolved disagreements were formulated but never used. Authors of selected articles for this review were contacted by email to glean additional information if required.

Quality assessments

Each study was evaluated according to the Newcastle Ottawa Scale for case-control and cohort studies and a modified version adapted for cross-sectional studies of the same scale was used (Supplement). The maximum score for cross-sectional studies was 10. Articles that were assigned with 9-to-10 stars were deemed to be of ‘High’ quality, while scores 7-to-8 were ascribed as being of ‘Moderate’ quality and scores 6
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or lower were deemed to be of ‘Low’ quality. The maximum score for both cohort
and case-control studies was nine. Articles that were assigned with values of 8-to-9
were classified as ‘High’ quality, while a score of 7 was assigned ‘Moderate’ quality
and ‘Low’ were assigned for studies with 6 or less stars.

Data Extraction

Data from each included study relating to: 1) author and year of publication, 2)
country of study, 3) sample size and population of focus, 4) study design, 5)
periodontitis case definition, 6) CKD definition, 7) statistical analysis approach and
crude/adjusted results were recorded into data extraction forms.

Statistical-analysis was conducted to address the two research questions
assessing bidirectional association between periodontal and kidney disease. Studies
that met the inclusion criteria and reported periodontal status were included in the
meta-analysis, irrespective of study design. Effect estimates reported in each study
were pooled collectively using odds ratios (ORs). To allow the greatest number of
studies to be included in the meta-analysis, effect estimates (e.g. risk ratio) were
converted to ORs if they reported any effect estimate other than odds ratio. Where
periodontitis was stratified by severity, data pertaining to the most severe definition
were included in the meta-analyses. Choice between random- and fixed-effect models
were decided based on estimated heterogeneity in each meta-analysis. Random-effect
models were preferred due to known heterogeneities in study designs, periodontal
disease case definitions or periodontal assessment methods prior to meta-analysis.
Funnel plot and Egger’s test were used to test for publication bias. Meta-regression
and subgroup analyses were employed to investigate whether study characteristics influenced between-study variability. All analyses were performed using the software Stata 13.1 (StataCorp, College Station, TX, USA).

RESULTS

Results of search

Figure 1 shows the flowchart for the search and study selection process. A total of 17 studies were selected and included of which nine studies reported periodontal disease as the exposure and CKD as the outcome.\textsuperscript{5, 25-32} Alternately, eight reported the association of CKD as the exposure and periodontal disease as the outcome\textsuperscript{33-40}.

Description of included studies

For brevity, unless otherwise indicated, all presentations of ORs herein are adjusted results. Specific details of variables that were included in the adjustment process for each study are included in the legends of Tables 1—2. Overall, eight of nine studies reporting associations between PD and CKD were judged to be of ‘high’ quality and one was deemed to be of ‘moderate’ quality using the NOS (Table 1 & Supplement Tables 4-6). Conversely, only two studies reporting on associations between CKD and PD were deemed to be of ‘high’ quality, while four were ‘moderate’ and two studies were considered to be of ‘low’ quality according to the NOS criteria (Table 2 and Supplement Tables 4-6).

GFR was consistently used between studies to diagnose CKD or ESRD. In contrast, an array of measures and classification criteria were used to assess
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periodontal disease. These included the Community Periodontal Index (CPI)\textsuperscript{29} or the CPI of Treatment Need (CPITN)\textsuperscript{26,39}, Periodontal Inflamed Surface Area (PISA)\textsuperscript{30}, Centres for Disease Control and American Academy of Periodontology (CDC-AAP)\textsuperscript{28,36,38}, American Academy of Periodontology 1999\textsuperscript{27}, European Federation of Periodontology\textsuperscript{28,38} or no formal disease classification\textsuperscript{5,25,31-35,37,40}.

Results of meta-analysis

For the association between periodontal disease and the outcome of CKD, the combined sample size across the studies was 141,920. Overall, pooled estimates from the nine included studies showed that individuals with periodontal disease had 1.60 (95% CI 1.44, 1.79) times higher odds of having CKD (Figure 2A). Following sensitivity analysis, studies which presented crude results independently revealed that individuals with periodontal disease had 1.80 (95% CI 1.15, 2.82) times higher odds of having CKD (Supplementary Figure 1A) while the magnitude of the association between periodontitis and CKD was attenuated when the analysis was limited to adjusted results 1.60 (95% CI 1.44, 1.79) (Supplementary Figure 1B).

The combined sample size of the association between CKD and the outcome of periodontal disease was 13,972. Pooled estimates from the eight included studies revealed a similar magnitude, but non-significant higher odds of having periodontal disease among people with CKD 1.69 (95% CI: 0.84, 3.40) (Figure 2B). We explored all methodological covariates as potential sources of heterogeneity in meta-regression analysis for the association between CKD and the outcome periodontal disease. Only statistical adjustment for confounding and study quality notably contributed to
heterogeneity (Supplement Table 1). The estimated OR for ‘high’ quality 1.50 (95% CI 1.10, 2.03) and ‘moderate’ quality studies OR 0.88 (95% CI 0.22, 3.48) served to attenuate the larger but-not-significant effect estimate produced by the two ‘low’ quality studies OR 6.74 (95% CI 0.45, 101.17) (Figure 2B). Pooled estimated effect sizes of smaller magnitude were also in studies that only presented crude estimates. Collectively, these methodological aspects explained approximately 35% of the heterogeneity between studies (Supplement Table 1).

The funnel plots for the association between periodontal disease as the exposure and CKD as outcome showed homogeneity (Figure 2C). Conversely, the association between CKD and periodontal disease exhibited significant heterogeneity $I^2 89.8\%$, $P=<0.01$ (Figures 2B & 2D). The Egger’s test for publication bias for both directions of association were non-significant (Figures 2C and 2D). Due to the small number of studies included in each meta-analysis, it is unclear whether this was due to lack of power or a true indication of publication bias.

**DISCUSSION**

This review reports evidence of a bi-directional association between periodontal disease and CKD. The methodological quality of included studies was relatively higher for those examining periodontal disease as the exposure and CKD as outcome compared to the converse association. Periodontitis has been implicated to influence a myriad of conditions including diabetes, hypertension, vascular disease and even difficulties in conception. Periodontal disease is highly prevalent, affecting a
quarter of the Australian adult population\textsuperscript{13} and up to half the U.S. adult population.\textsuperscript{12} Likewise, it is estimated that 15\% of U.S. adults have CKD\textsuperscript{45} while in Australia, biomedical results from the most recent national health survey estimate that 10\% of adults, equivalent to 1.7 million people have CKD.\textsuperscript{2} Given that both conditions share common risk factors, positive associations are unsurprising.

Unlike criteria used to distinguish the presence of CKD,\textsuperscript{2} defining and classifying periodontal disease has been contentious\textsuperscript{46} leading to differences in its diagnosis across the world. Consequently, an array of criteria has been developed describing historical disease experience (CAL), current disease processes (PPD and BOP), which sites in the mouth should be assessed, and how. In order to incorporate as many studies as possible in the meta-analyses, we elected to include studies if the periodontal status was clinically measured rather than limiting to a particular periodontitis case definition. In doing so, this was at the expense of homogeneity in the meta-analyses. While all studies included in the periodontal disease and CKD association meta-analysis had specified case definitions for periodontitis, four of the eight studies included in the CKD and periodontal disease association meta-analysis did not use a formal case definition.

The association between CKD and periodontal disease may have been influenced by the level of impaired renal function. In this meta-analysis, a pragmatic approach to combine all stages of CKD into a single ‘diseased’ group may have inflated the effect estimate given than half of the studies included in the meta-analysis involved ESKD patients with GFR levels at or below 15 mL/min/1.73m\textsuperscript{2}. Patients
with ESKD have repeated bouts of uremic syndrome when not dialyzed which, in turn, impairs the normal immune function of monocytes and polymorphonuclear lymphocytes. Consequently, overgrowth of periodontopathic bacteria in the presence of ESKD is possible. Studies by Takeuchi et al. and Bastos and colleagues both reported that the periodontopathogens *Tannarella forsythia* and *Treponema denticola*, were more often detected within the periodontal tissues of haemodialysis patients compared to their respective non-CKD control groups. Further, the concentration of *T. forsythia*, *Porphyromonas gingivalis*, *Prevotella intermedia* and *Prevotella nigrescens* were significantly higher among haemodialysis patients compared to non-CKD controls in the study by Castillo and colleagues. Of interest, stratification by extent of loss of periodontal attachment (LPA) <3mm among the haemodialysis group revealed that there were no significant differences in the concentrations of *T. forsythia*, *P. gingivalis* or *P. intermedia* when comparing individuals with low levels of LPA against those expressing high levels of disease. This suggests that differences may not be due to periodontal disease per se but rather that renal disease influences bacterial composition.

A strength of the present review are the sample sizes of the two meta-analyses. The large sample sizes are mostly attributed to the investigations which used representative survey data of the general populations in the USA, South Korea and Taiwan. Secondly, the systematic and methodical approach invested in formulating the search strategies for each of the four databases ensured that all potential studies eligible for inclusion were incorporated in this review. It was not

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pragmatic to search for articles that were published in languages other than English. For this reason, the possibility that potential publications were missed during the search process cannot be discounted. However, the 17 papers included in this review arose from nine different countries, seven of which do not have English as their official language. Therefore, the potential impact of excluding non-English publications may have been negligible. The internal validity and generalizability of the meta-analysis summarizing the association between periodontal disease and CKD is likely to be high on account that it was largely composed of adjusted estimates from each included study. Thus, it is expected that the influence of residual confounding would be minimal. Alternatively, adjusted estimates from the two studies included in the CKD and periodontal disease association are conceivably too few to make that meta-analysis externally valid.

Cohort studies from Japan, Taiwan, and the U.S. have shown that periodontal disease is associated with the incidence of CKD, or decline in renal function. This builds on the present finding which estimates that periodontal disease imparts a 60% higher odds of having CKD. Diagnosis, treatment and management of patients with periodontitis should form part of routine dental care for all people. The evidence presented herein indicates that patients with suspected or confirmed CKD may benefit from undergoing a periodontal assessment and receiving treatment if a positive diagnosis is made. Despite no studies to date having investigated the incidence or progression of periodontal disease among CKD patients, and given the shared risk factors for both conditions, it would be advisable that periodontal care
form part of the standard CKD management regimen. Future research should aim to
determine whether providing periodontal treatment will result in improved GFR,
particularly among those with early evidence of impaired renal function. Current
efforts in this venture have, for various reasons, been equivocal. 25, 52-56

CONCLUSION:
We find moderate evidence in association to the presence of PD in CKD patients
while the evidence for the opposite direction is extremely weak. Given that the studies
included in this review were all observational, the level of evidence can be considered
‘low’ at best. Inconsistencies in the criteria used to define periodontitis and in the
selection of study participants hamper comparisons. Given that chronic inflammation
among patients with CKD and ESKD exacerbates health concerns in this population,
pragmatic measures to reduce systemic inflammation, such as periodontal treatment,
may have long-term benefits. Additional studies among patients with periodontitis
and CKD which measure GFR prospectively are required to further understand
potential causative mechanisms.

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KK developed the search criteria, conducted the database and hand-searches, extracted data and prepared the manuscript as the corresponding author. MB conducted the database searches and was involved in screening articles for inclusion in addition to assisting in manuscript preparation. AS and GN conducted the meta-analysis and wrote the statistical methods section of this paper. Each co-author contributed important intellectual content during manuscript drafting or revision. KK accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KK takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study have been explained.

SUPPORT AND FINANCIAL DISCLOSURE DECLARATION

KK is supported by NHMRC Early Career Fellowship #1113098 and reports no conflicts of interest. MB is supported by Universidade Federal do Rio Grande do Sul and has no commercial or associative interests that represents a conflict.
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46 Savage A, Eaton KA, Moles DR, Needleman I. A systematic review of definitions of periodontitis and methods that have been used to identify this disease. Journal of Clinical Periodontology. 2009; 36: 458-67.
FIGURE LEGEND

FIGURE 1: Flow diagram of the search process

FIGURE 2A: Forrest plot for the association between periodontal disease and the outcome of chronic kidney disease, stratified according to appraisal quality scores

FIGURE 2B: Forrest plot showing the association between chronic kidney disease and the outcome of periodontal disease, stratified according to appraisal quality scores

FIGURE 2C: Funnel plots demonstrating the degree of bias and heterogeneity within the analysed studies for the association between periodontal disease and the outcome of chronic kidney disease

FIGURE 2D: Funnel plots demonstrating the degree of bias and heterogeneity within the analysed studies for the association between chronic kidney disease and the outcome of periodontal disease
### Table 1: Periodontal disease associated with CKD

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Setting</th>
<th>Sample Size</th>
<th>Study Design</th>
<th>CKD Definition</th>
<th>PD Definition</th>
<th>Analytical Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artese et al. 2010&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Brazil</td>
<td>40 subjects in total CKD (pre-dialysis) n=21 Non-CKD control n=19</td>
<td>Quasi-experimental study</td>
<td>CKD: GFR between 89 and 15mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>PD: 4 sites in 3 different teeth with CAL e 4 mm &amp; BOP.</td>
<td>Chi sq and Wilcoxon signed-rank test</td>
</tr>
<tr>
<td>Chen et al 2015&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Taiwan</td>
<td>Total 100,263 Taiwan residents PD: n = 13,749 Non-PD: n = 86,514</td>
<td>Prospective cohort</td>
<td>e 30% decline in eGFR.</td>
<td>CPITN</td>
<td>Multivariable logistic regression modelling</td>
</tr>
<tr>
<td>Fisher et al 2008&lt;sup&gt;5&lt;/sup&gt;</td>
<td>USA</td>
<td>12,947 adults (NHANES III) PD n=1,271 Non-PD n=10,066 Edentulous n=1,610</td>
<td>Cross-sectional</td>
<td>GFR between 60mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt; &amp; e 15mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>e 1 site with e 4mm LOA + BOP</td>
<td>Multivariable logistic regression modelling</td>
</tr>
<tr>
<td>Grubbs et al 2011&lt;sup&gt;27&lt;/sup&gt;</td>
<td>USA</td>
<td>6,199 adults aged ≥ 21 and d75 years NHANES 2001-2004 Mod/Severe PD n = ~329</td>
<td>Cross-sectional</td>
<td>GFR between 60mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt; &amp; e 15mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>e 2 IP sites with e 3 mm CAL &amp; e 2 IP sites with e 4mm PPD or e 1 site with PPD e 5 mm.</td>
<td>Chi sq and Multivariate correlations</td>
</tr>
<tr>
<td>Grubbs et al 2016&lt;sup&gt;29&lt;/sup&gt;</td>
<td>USA</td>
<td>761 men aged ≥ 65 years</td>
<td>Retrospective cohort</td>
<td>Incident eGFR&lt;60mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt; &amp; e 5% decline in eGFR</td>
<td>European Workshop &amp; CDC/AAP “severe” classifications</td>
<td>Multivariable Poisson regression</td>
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<tr>
<td>Han et al 2013&lt;sup&gt;27&lt;/sup&gt;</td>
<td>South Korea</td>
<td>15,729 adults participating in the Korean NHANES</td>
<td>Cross-sectional</td>
<td>GFR &lt;60mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CPI score e 3 in any index teeth</td>
<td>Multivariate logistic model</td>
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</table>
Table 1: Periodontal disease associated with CKD (cont.)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Effect size and Crude Association with 95%CI</th>
<th>Adjusted effect</th>
<th>Variables used in adjusted models</th>
<th>NOS quality assessment</th>
</tr>
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<tbody>
<tr>
<td>Iwasaki et al 2012</td>
<td></td>
<td></td>
<td>Healthy/gingivitis</td>
<td>High</td>
</tr>
<tr>
<td>Kshirsagar et al 2005</td>
<td>5,537 individuals from ARIC study (US)</td>
<td>Cross-sectional</td>
<td>GFR&lt;60mL/min/1.73m²</td>
<td>Healthy/gingivitis</td>
</tr>
<tr>
<td></td>
<td>Healthy/Gingivitis n=2,314</td>
<td></td>
<td>Initial: e2 IP sites e 4mm of CAL (not on the same tooth)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial PD n=2,276</td>
<td></td>
<td>Severe: e2 IP (not on the same tooth) with a CAL e 6 mm and e 1 PPD of e 5mm.</td>
<td></td>
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<tr>
<td></td>
<td>Severe PD n=947</td>
<td></td>
<td>Multivariate logistic model</td>
<td></td>
</tr>
<tr>
<td>Kshirsagar et al 2007</td>
<td>154 hemodialysis patients.</td>
<td>Cross-sectional</td>
<td>ESKD GFR d15mL/min/1.73m²</td>
<td>Severe periodontitis: e 60% of sites with CAL e 4 mm</td>
</tr>
<tr>
<td>Study Reference</td>
<td>Group Comparison</td>
<td>Relative Risk (Confidence Interval)</td>
<td>Adjusted Relative Risk (Confidence Interval)</td>
<td>Covariates</td>
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<tr>
<td>Fisher et al 2008&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Non-PD (ref) OR 1.26 (0.78 to 2.03)</td>
<td>Non-PD (ref) Adj OR 1.20 (0.76 – 1.90)</td>
<td>Age, gender, tobacco, race, hypertension, annual physician visit, LDL, macroalbuminuria, income, high total cholesterol, hospitalisation within past year.</td>
<td>High</td>
</tr>
<tr>
<td>Grubbs et al 2011&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Non-PD/mild PD (ref) OR 2.50 (1.96 to 3.19)</td>
<td>Non-PD/mild PD (ref) Adj OR 1.51 (1.13 – 2.02)</td>
<td>Age, gender, tobacco, diabetes, hypertension, race, educational attainment, poverty status &amp; dental care use.</td>
<td>High</td>
</tr>
<tr>
<td>Grubbs et al 2016&lt;sup&gt;24&lt;/sup&gt;</td>
<td>European Workshop IRR 2.42 (1.45–4.02)</td>
<td>European Workshop Adj IRR 2.04 (1.21 – 3.44)</td>
<td>Age, diabetes, hypertension, tobacco use, race and education.</td>
<td>High</td>
</tr>
<tr>
<td>Han et al 2013&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Non-PD (ref) OR 4.07 (3.11 to 5.33)</td>
<td>Non-PD (ref) OR 1.39 (1.03-1.89)</td>
<td>Age, sex, region, education, obesity, smoking, exercise, hypertension, diabetes, hypercholesterolemia, CVD</td>
<td>High</td>
</tr>
<tr>
<td>Iwasaki et al 2012&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Highest PISA vs PISA quartiles 1-3 Decreased eGFR OR 2.58 (1.34 to 4.98)</td>
<td>Highest PISA vs PISA quartiles 1-3 Decreased eGFR Adj OR 2.24 (1.05 – 4.79)</td>
<td>Age, smoking, dental visiting pattern, hyperglycaemia, hypoalbuminemia</td>
<td>Moderate</td>
</tr>
<tr>
<td>Kshirsagar et al 2005&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Healthy/Gingivitis (ref) Initial PD: OR 2.10 (1.33-3.31)</td>
<td>Healthy/Gingivitis (ref) Initial PD: Adj OR 2.00 (1.23 –</td>
<td>Age, ARIC field centre, race, sex, diabetes, hypertension, BMI, education level, 5-level smoking</td>
<td>High</td>
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<tr>
<td>Kshirsagar et al 2007</td>
<td>Severe PD: OR 2.21 (1.28-3.82)</td>
<td>3.24)</td>
<td>Severe PD: Adj OR 2.14 (1.19 – 3.85)</td>
<td>status and serum CRP.</td>
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<tr>
<td>Non-periodontitis/mild/moderate ref</td>
<td>Non-periodontitis/mild/moderate ref</td>
<td>Non-periodontitis/mild/moderate ref</td>
<td>Non-periodontitis/mild/moderate ref</td>
<td>Non-periodontitis/mild/moderate ref</td>
</tr>
<tr>
<td>Severe PD: OR 3.23 (1.16 to 8.96)</td>
<td>Severe PD: Adj OR 8.20 (1.61 – 41.82)</td>
<td>Severe PD: Adj OR 8.20 (1.61 – 41.82)</td>
<td>Severe PD: Adj OR 8.20 (1.61 – 41.82)</td>
<td>Severe PD: Adj OR 8.20 (1.61 – 41.82)</td>
</tr>
<tr>
<td>Age, gender, race, diabetes, hypertension, BMI, smoking, study site, nPCR, serum calcium, serum phosphorus and total cholesterol.</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

**Abbreviations:** GFR: glomerular filtration rate; CKD: chronic kidney disease; ESKD: end-stage kidney disease; CRP: C-reactive protein; PPD: probing pocket depth; CAL: clinical attachment level; IP: interproximal; NHANES: National Health and Nutritional Examination Survey; ARIC: Atherosclerosis Risk in Communities Study; CDC/AAP: Centres for Disease Control and Prevention and American Academy of Periodontology; EFP: European Federation of Periodontology; PD: periodontal disease; Chi Sq: chi square.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Setting</th>
<th>Sample Size</th>
<th>Study Design</th>
<th>CKD Definition</th>
<th>PD Definition</th>
<th>Analytical Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastos et al 2011</td>
<td>Brazil</td>
<td>66 chronic periodontal patients in total</td>
<td>Case-control</td>
<td>Presence of albuminuria, glomerular hematuria, structural abnormalities or GFR &lt;60mL/min/1.73m</td>
<td>e 2 teeth with e 6mm CAL &amp; e 1 site with e 5mm PPD.</td>
<td>t-test</td>
</tr>
<tr>
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</tr>
<tr>
<td>Garcez et al 2009</td>
<td>Spain</td>
<td>160 total Reduced GFR : n=80 Healthy GFR: n=80</td>
<td>Case-control</td>
<td>GFR &lt;60 &amp; d 89 mL/min/1.73m</td>
<td>No case definition. Ramfjord teeth examined</td>
<td>t-test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gavalda et al 1999</td>
<td>Spain</td>
<td>Hemodialysis patients n=105 Healthy controls n=53</td>
<td>Case-control</td>
<td>ESKD GFR d 15 mL/min/1.73m</td>
<td>No case definition used</td>
<td>t-test</td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>
| Ioannidou & Swede 2011   | USA              | 12,081 adults e 21 and d 60 years (NHANES III)                             | Cross-sectional       | GFR <15 & d 89 mL/min/1.73m                                                   | CDC/AAP Moderate 
|                         |                  |                               |                       |                                                                                 | e 2 IP sites with e 3 mm CAL & e 2 IP sites with e 4mm 
|                         |                  |                               |                       |                                                                                 | PPD or e 1 site with PPD e 5 mm.                                               |                     |
|                         |                  |                               |                       |                                                                                 |                                                                                |                     |

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<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Study Design</th>
<th>GFR Definition</th>
<th>Case Definition</th>
<th>Statistical Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marakoglu et al 2003</td>
<td>Turkey</td>
<td>72 subjects in total; Hemodialysis n=36; Systemically healthy periodontitis n=36</td>
<td>Cross-sectional</td>
<td>ESKD GFR d15mL/min/1.73m²</td>
<td>No formal case definition</td>
<td>t-test &amp; ANOVA</td>
</tr>
<tr>
<td>Sharma et al 2014</td>
<td>United Kingdom</td>
<td>469 patients with stage e3 CKD in total; Dentate n=389; Edentulous n=80; ADHS cohort n=876</td>
<td>Cross-sectional</td>
<td>GFR &lt;60mL/min/1.73m²</td>
<td>CDC/AAP &amp; EFP case definitions; Moderate: e 1 tooth with PD e4mm; Severe e 1 tooth with PD e6mm</td>
<td>chi square &amp; multivariable logistic regression</td>
</tr>
<tr>
<td>Tiwari et al 2013</td>
<td>India</td>
<td>60 participants in total; 30 CKD on dialysis; 30 age &amp; sex-matched systemically healthy controls</td>
<td>Case-control</td>
<td>ESKD GFR d15mL/min/1.73m²</td>
<td>CPITN</td>
<td>t-test</td>
</tr>
<tr>
<td>Torres et al 2010</td>
<td>Brazil</td>
<td>30 participants in total; 16 ESKD patients on dialysis; 14 Systemically healthy periodontitis patients</td>
<td>Case-control</td>
<td>ESKD GFR d15mL/min/1.73m²</td>
<td>No case definition used</td>
<td>t-test</td>
</tr>
</tbody>
</table>
Table 2: Observational Studies: CKD associated with Periodontitis (cont.)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Effect size and Crude Association with 95%CI</th>
<th>Adjusted effect</th>
<th>Variables used in adjusted models</th>
<th>NOS quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastos et al 2011</td>
<td>Pre-dialysis group had significantly higher extent of PPD &lt; 5mm (21.8 ± 23.4) than non-CKD patients (8.3 ± 7.7) but not RRT patients (14.1 ± 14.6). RRT group had significantly higher extent of CAL &lt; 6mm 26.7 ± 27.8 compared to non-CKD 6.7 ± 8.5.</td>
<td>Not reported</td>
<td>N/A</td>
<td>Moderate</td>
</tr>
<tr>
<td>Garcez et al 2009</td>
<td>mean PPD: Decreased GFR (0.65 ± 0.75) versus control (0.56 ± 0.79); mean CAL: Decreased GFR (0.54 ± 0.60) versus control (0.44 ± 0.56)</td>
<td>Not reported</td>
<td>N/A</td>
<td>Moderate</td>
</tr>
<tr>
<td>Gavalda et al 1999</td>
<td>There was no significant difference in mean LPA between Hemodialysis group mean (4.9 ± 2.1) versus (4.2 ± 2.5).</td>
<td>Not reported</td>
<td>N/A</td>
<td>Low</td>
</tr>
<tr>
<td>Ioannidou &amp; Swede 2011</td>
<td>Non-CKD ref Non-Hispanic Blacks OR 1.85 (1.48 – 2.30) Mexican American OR 2.77 (2.15 – 3.55)</td>
<td>Non-CKD ref</td>
<td>Non-Hispanic Blacks Adj OR 1.24 (0.95 – 1.62) Mexican American Adj OR 1.59 (1.14 – 2.13)</td>
<td>High</td>
</tr>
<tr>
<td>Marakoglu et al 2003</td>
<td>No significant differences between groups in terms of mean PPD (HD 1.8 ± 0.6 vs control 1.8 ± 0.6). No difference in frequency of PPD 3-6 mm between groups (both 8%). Control group had more participants with PPD&lt; 6mm (11%) compared to</td>
<td>Not reported</td>
<td>N/A</td>
<td>High</td>
</tr>
<tr>
<td>Study</td>
<td>HD group (0%)</td>
<td>ADHS ref. vs whole RIISC cohort.</td>
<td>ADHS ref. vs whole RIISC cohort.</td>
<td>Age, gender, ethnicity, smoking status, SES.</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Tiwari et al 2013</td>
<td>No significant difference in PPD between groups: ESKD mean 5.53 ± 2.53 compared to healthy controls 1.86 ± 1.26.</td>
<td>No significant difference in PPD between groups: ESKD mean 5.53 ± 2.53 compared to healthy controls 1.86 ± 1.26.</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td>Torres et al 2010</td>
<td>Mean pocketing was significantly lower in ESKD group (1.77 ± 0.32) compared to periodontitis control group (2.65 ± 0.53).</td>
<td>Mean pocketing was significantly lower in ESKD group (1.77 ± 0.32) compared to periodontitis control group (2.65 ± 0.53).</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Abbreviations:** GFR: glomerular filtration rate; CKD: chronic kidney disease; ESKD: end-stage kidney disease; CRF: Chronic Renal Failure; RRT: renal replacement therapy; HD: Hemodialysis; CAPD: Continual Ambulatory Peritoneal Dialysis; CRP: C-reactive protein; PPD: probing pocket depth; CAL: clinical attachment level; LPA: loss of periodontal attachment; IP: interproximal; BOP: bleeding on probing; CPI/TN: Community Periodontal Index of Treatment Needs; NHANES: National Health and Nutritional Examination Survey; ARIC: Atherosclerosis Risk in Communities Study; ADHS: Adult Dental Health Study; RIISC: Renal Impairment in Secondary Care cohort study; CDC/AAP: Centres for Disease Control and Prevention and American Academy of Periodontology; EFP: European Federation of Periodontology; PD: periodontal disease.
FIGURE 1: Flow diagram of the search process

- Titles from PubMed (n=1,229)
- Titles from EMBASE (n=1,270)
- Titles from Web of Science (n=108)
- Scopus (n=1,448)

Total records (n=4,055)

- Records excluded based on paper titles/duplicates (n=3,945)

Number screened for inclusion (n=110)

- Records excluded based on abstract (n=54)

Full-text articles assessed for eligibility (n=56)

- Cohort/intervention studies not in meta-analysis (n=32)

- Records excluded outright (n=7)

- Studies included in quantitative synthesis (n=17)
  - CKD exposure on periodontitis: (n=9)
  - Periodontitis exposure on CKD: (n=8)
FIGURE 2A: Forrest plot for the association between periodontal disease and the outcome of chronic kidney disease, stratified according to appraisal quality scores

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al 2015</td>
<td>1.59 (1.37, 1.86)</td>
<td>53.39</td>
</tr>
<tr>
<td>Fisher et al 2008</td>
<td>1.20 (0.76, 1.90)</td>
<td>5.94</td>
</tr>
<tr>
<td>Grubbs et al 2011</td>
<td>1.51 (1.13, 2.02)</td>
<td>14.79</td>
</tr>
<tr>
<td>Grubbs et al 2015</td>
<td>4.18 (1.68, 10.39)</td>
<td>1.50</td>
</tr>
<tr>
<td>Grubbs et al 2016</td>
<td>2.04 (1.21, 3.44)</td>
<td>4.57</td>
</tr>
<tr>
<td>Han et al 2013</td>
<td>1.39 (1.03, 1.89)</td>
<td>13.55</td>
</tr>
<tr>
<td>Kshirsagar et al 2005</td>
<td>2.14 (1.19, 3.85)</td>
<td>3.62</td>
</tr>
<tr>
<td>Kshirsagar et al 2007</td>
<td>8.20 (1.61, 41.82)</td>
<td>0.47</td>
</tr>
<tr>
<td>Subtotal (I-squared = 43.6%, p = 0.088)</td>
<td>1.59 (1.42, 1.78)</td>
<td>97.83</td>
</tr>
</tbody>
</table>

Moderate

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwasaki et al 2012</td>
<td>2.24 (1.05, 4.79)</td>
<td>2.17</td>
</tr>
<tr>
<td>Subtotal (I-squared = .%, p = .)</td>
<td>2.24 (1.05, 4.78)</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Heterogeneity between groups: p = 0.384
Overall (I-squared = 39.2%, p = 0.106) | 1.60 (1.44, 1.79) | 100.00 |
FIGURE 2B: Forrest plot showing the association between chronic kidney disease and the outcome of periodontal disease, stratified according to appraisal quality scores.
FIGURE 2C: Funnel plots demonstrating the degree of bias and heterogeneity within the analysed studies for the association between periodontal disease and the outcome of chronic kidney disease

Egger’s test for publication bias: P=0.921
FIGURE 2D: Funnel plots demonstrating the degree of bias and heterogeneity within the analysed studies for the association between chronic kidney disease and the outcome of periodontal disease

Egger’s test for publication bias: $P=0.688$
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Kapellas, K; Singh, A; Bertotti, M; Nascimento, GG; Jamieson, LM; Hughes, J; Sajiv, C; Fernandes, D; Pawar, B; Harris, D; Hoy, W; Cass, A; Maple-Brown, L; Brown, A; Skilton, M; Askie, L; Bartold, PM; Arrow, P

Title:
Periodontal and chronic kidney disease association: A systematic review and meta-analysis

Date:
2019-02-01

Citation:

Persistent Link:
http://hdl.handle.net/11343/285384