



PERIODONTAL DISEASE AND ITS ASSOCIATION WITH CHRONIC DISEASE: A LITERATURE REVIEW

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ABSTRACT

Background

The aim of this article is to review various studies aimed at finding the association between Periodontitis and Chronic Kidney Disease.

Methods

A search was conducted for all the articles in the past that have studied the association between Periodontitis and Chronic Kidney Disease. Data sources primarily included Pub Med with MeSH terms and free text, Scopus and Cochrane library, Google Scholar and Copernicus.

In addition, a hand search of selected periodontal journals and review articles was conducted.

Result

Almost all the work in this direction has developed in the last decade. Majority of the articles suggest a strong positive association between the two. Non-surgical Periodontal treatment seems to improve kidney functions in affected persons. A couple of studies, though, have found no associations between periodontal disease with alterations in kidney functions.

KEYWORDS : Periodontal Disease, Chronic Kidney Disease(CKD), Glomerular Filtration rate(GFR), Oral health.



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INTRODUCTION

Periodontal disease

Periodontal diseases are chronic, predominantly gram negative infections of the oral cavity that are initiated in the gingiva and if untreated lead to alveolar bone destruction and eventual tooth loss. Severe periodontitis is found in 5-15% of most populations. Juvenile or early onset aggressive periodontitis that leads to premature tooth loss affects about 2% of the youth.¹ In the last 30 years there has been a lot of research on the pathogenesis of periodontitis and we now understand that the host response to the organisms causing periodontitis varies between individuals. Certain systemic disorders and conditions alter host tissues and physiology which may impair host barrier integrity and host defense to periodontal infection resulting in more destructive disease. In the past two decades a field of periodontal research, known as Periodontal Medicine has emerged investigating the link between periodontal disease and other systemic diseases.

There is enough evidence to suggest that periodontal infections can adversely affect systemic health with manifestations such as coronary heart disease(CHD) and CHD-related events such as angina and infarction, atherosclerosis, stroke, diabetes mellitus, preterm labor, low birth weight delivery and respiratory diseases.²

In the last decade there has been an increasing evidence to show association between periodontitis and chronic kidney disease.

Kidneys

Kidneys are one of the most important organs of the body whose functional unit is a nephron. Its main components are the glomerulus, the proximal convoluted tubules(PCT), loop of Henle, distal convoluted tubules(DCT) and collecting duct. Kidneys have multiple functions such as excretion of nitrogenous waste products and foreign chemicals, control of blood pressure, maintaining the electrolyte and water balance, regulation of acid-base

balance, controlling osmolarity of body fluid and concentration of electrolytes, secretion, excretion and metabolism of hormones.

Kidneys allow us to consume a variety of foods, drugs, vitamins and supplements, additives and excess fluids without worry that toxic by-products will build up to harmful levels. The kidneys also regulate levels of various minerals such as calcium, sodium and potassium in the blood. Kidneys also produce certain hormones, which have important functions in the body, such as synthesis of active form of Vitamin D (Calcitriol), Erythropoietin(EPO) and Renin.³

Chronic Kidney Diseases (CKD)

CKD also known as chronic renal disease is a progressive loss in renal function over a period of months or years. The symptoms of worsening kidney function are unspecific and might include feeling generally unwell and experiencing a reduced appetite. Often, the disease is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with hyper tension and diabetes and those with a blood relative with CKD.

CKD is identified by a blood test for creatinine. Higher levels of creatinine indicate a falling Glomerular Filtration Rate(GFR) and as a result a decreased capability of the kidneys to excrete waste products. Creatinine levels may be normal in early stages of CKD. Recent professional guidelines classify the severity of CKD in 5 stages, with stage 1 being the mildest and usually causing few symptoms and stage 5 being a severe illness with poor life expectancy if untreated. Stage 5 CKD is also called established CKD and is synonymous with now outdated terms End Stage Renal Disease(ESRD), Chronic Kidney Failure(CKF) or Chronic Renal Failure(CRF). The most common causes of CKD are Diabetes Mellitus(DM), hypertension and glomerulonephritis. Together, they cause approximately 75% of all adult cases.

Stages of CKD ⁴

Stage	Description	GFR(ml/min/1.73m ²)
1	Slightly diminished function, kidney damage with normal or relatively high GFR	≥ 90
2	Mild decrease in Kidney function	60-89
3	Moderate decrease in Kidney function	30-59
4	Severe decrease in Kidney function (Preparation for renal replacement therapy)	15-29
5	Established kidney failure (Permanent renal replacement therapy)	≤ 15

The normal range of GFR is in the range of 100-130ml/min/1.73m²(adjusted for body surface area, so similar in men and women). After 40 years of age, GFR decreases progressively with age, by about 0.4-1.2ml/min/year.

Periodontitis and Chronic Kidney Disease

Evidence on the prevalence of periodontitis in Chronic Kidney Disease patients is conflicting. In a cross-sectional study of 45 dialysis patients, Naugle and co-workers found that 100% of the subjects displayed some form of periodontal disease although majority of the patients(64%) had mild Periodontitis or gingivitis.⁵

Marakoglu et al found no difference in the clinical parameters of periodontal disease between 36 chronic renal failure patients on hemodialysis and 36 age and gender matched healthy controls. The authors inferred that chronic renal failure did not seem to be a risk factor for more severe periodontal destruction in renal failure patients compared to general population⁶.

The Colgate Oral Care Report feature article "Periodontitis and Renal Disease" discusses five studies, three with findings suggesting an association between Periodontitis and Renal Diseases and two which suggest no association⁷.

Chronic Kidney Disease subjects are characterized by some well established risk

factors of Periodontal Disease such as poor oral hygiene and diabetes. Because of this conflicting available evidence, it was our goal to further explore the available literature for this article.

REVIEW OF LITERATURE

Lacson & Levin in one of the earlier studies in the ESRD population have concluded that C-Reactive Protein(CRP) is useful in prognosis and monitoring the response to therapy. They have recommended a careful search for infections in dialysis patients with special attention to vascular access sites, periodontitis and other potentially chronic and covert infections⁸.

Kshirsagar AV et al in a cross-sectional study of 5,537 middle aged black and white men and women, found that, initial and severe periodontal disease is more associated with GFR <60ml/min/1.73 m² and elevated serum creatinine levels than with healthy controls. This claims to be the first study to show the association of Periodontal Disease with prevalent renal insufficiency.⁹ This study has been followed by studies that have tried to examine the association between Periodontitis and CKD from different perspectives.

Jacek Borawski et al examined the periodontal status of pre-dialysis CKD and maintenance dialysis patients and their results indicate high severity of periodontitis in all renal failure groups as compared to general population

subjects. They concluded that periodontitis is prevalent, severe and under-recognized in renal failure patients. Prophylaxis and early dental treatment should be intensified in these subjects.¹⁰

Wendy A Shultis et al studied the effect of Periodontitis on overt nephropathy and ESRD in Type 2 diabetes. They followed 529 individuals (≥ 25 years) with Type 2 Diabetes, $eGFR \geq 60$ ml/min/1.73m² and no macroalbuminuria for up to 22 years until the development of macroalbuminuria or ESRD. They found that periodontal disease predicts development of overt nephropathy and ESRD in individuals with Type-2 diabetes.¹¹

Kshirsagar AV et al studied another aspect when they measured serum albumin levels in ESRD patients. They found that after adjustment for other variables, severe periodontal disease was associated with low serum albumin compared to individuals without severe periodontal disease. They found no observed association of severe periodontal disease with CRP.¹²

In an effort to examine the possible link of kidney disease with serum antibody to oral pathogens, Kshirsagar AV et al assessed periodontal disease status in an older community dwelling population and found that high levels of serum IgG to selected periodontal pathogens including *P.gingivalis*, *T.denticola* and *Actinobacillus actinomycetemcomitans* were associated with increased odds for $eGFR < 60$ ml/min/1.73m². They concluded that elevated IgG to periodontal pathogens is significantly associated with impaired kidney function, independent of traditional risk factors.¹³

Monica A Fisher et al performed a cross sectional study of 12,947 adults (≥ 18 years of age) to measure kidney function, periodontal status and other traditional and non-traditional risk factors for CKD. Their results showed that adults with periodontal disease and edentulous arches were twice as likely to have CKD after simultaneously adjusting for other traditional and non-traditional risk factors. They have

concluded that identifying individuals with periodontal disease and inclusion of periodontal therapy could be an approach to impede the increasing number of individuals with CKD.¹⁴

Monica A Fisher et al in their study titled "Clinical and Serologic markers of periodontal infection and CKD" found that adults with high *Actinobacillus actinomycetemcomitans* (Aa) antibody titer were less likely to have CKD and those with edentulism were more likely to have CKD.¹⁵

Kshirsagar AV et al in a retrospective analysis of 168 adult patients to study association between periodontal disease and cardiovascular disease mortality in out-patients on hemodialysis, found that moderate to severe periodontal disease, compared to mild or no periodontal disease, was significantly associated with death from cardiovascular causes though they concluded that larger studies are needed to confirm this connection.¹⁶

Bastos JA et al studied the severity of periodontal disease and identification of microorganisms in subgingival plaque in patients with and without CKD. Their results showed that chronic periodontal disease was more severe in patients with CKD.

A strong association was observed between frequency of *C.albicans*, *P.gingivalis*, *T.denticola* and Clinical Attachment Loss (CAL) when CKD patients were compared with control group.¹⁷

Artese HP et al found that CKD pre-dialysis patients show a good response to non-surgical periodontal treatment. In fact, their study found that even individuals without clinical evidence of chronic periodontitis showed statistically significant improvement in GFR.¹⁸

Vilela EM et al reported the effect of the periodontal treatment on patients with CKD and found that the treatment resulted in significant reductions in highly specific CRP, Inter Leukin (IL-6) and prohepcidin levels,

when these inflammatory markers were evaluated before and 3 months after treatment. They concluded that successful periodontal treatment may represent an important means of ameliorating the inflammatory burden seen in patients with CKD.¹⁹

Monica A Fisher et al assessed the potential for connection between CKD and periodontal disease and mediators of these relationships using structural equation models of data from 11,211 adults (≥ 18 yrs of age). Their analyses support a bidirectional relationship between CKD and periodontal disease mediated by hypertension and the duration of diabetes.²⁰

Grubbs V et al did a cross-sectional analysis to check whether association between CKD and periodontal disease is similar across various populations. They reported that estimated prevalence of moderate/severe periodontal disease and CKD were 5.3% and 10.6% respectively. Periodontal Disease was associated with more than twofold higher risk of CKD irrespective of race/ethnicity.²¹

Lawrence T Glickman and coworkers in a period from 2002 to 2008 studied an cohort of 164,706 dogs with periodontal disease and a cohort of age matched dogs with no periodontal disease and compared them for incidence of azotemic CKD. They found that with increasing severity of periodontal disease, the hazard ratio for azotemic CKD increased and this was also associated with serum creatinine > 1.4 mg/dl and Blood Urea Nitrogen (BUN) > 36 mg/dl.²²

E. Ioannidou and H Swede in their article titled "Disparities in Periodontitis prevalence among Chronic Kidney Disease patients" hypothesized that CKD patients would have higher prevalence of chronic periodontal disease compared to non-CKD individuals. They also studied whether the prevalence varied by race in Non-Hispanic whites, non-Hispanic blacks as well as Mexican-Americans. Moderate periodontal disease was significantly more prevalent in CKD as compared to non-CKD cases. It claims to be the first report of a true prevalence study of periodontal disease in CKD populations using NHANES III data.²³

Pradeep A R et al in a case controlled study, divided 60 subjects into 3 groups, i.e. healthy, CKD and CKD with periodontal disease. The plasma samples were quantified for Pentraxin-3 levels (PTX-3) which is a classic mediator of inflammation and markers of acute phase reactions. Both groups with CKD had higher plasma PTX-3 than the healthy controls. PTX-3 correlated with periodontal parameters indicating that these values could be used for identifying individuals with PD at higher risk of CKD.²⁴

E. Ioannidou et al in a recently published article concluded that when periodontitis is used as an independent variable there is a strong association between extent of periodontal disease and serum CRP levels in patients with CKD.²⁵

F Brito et al looked at the extent and severity of chronic periodontitis in CKD patients and found that pre-dialysis and hemodialysis patients are associated with higher prevalence of severe periodontitis compared with healthy individuals and Continuous Ambulatory Peritoneal Dialysis (CAPD).²⁶

All these studies seem to be emphatically pointing to a strong association between periodontal disease and CKD. Amidst this mounting evidence favouring the association, is a study published by Renata S Brotto et al, which assessed 60 healthy non-smokers (30 with and 30 without periodontal disease) for markers of kidney functions and found that none of the markers revealed significant difference between control and test groups. All measured values fell within reference levels leading them to conclude that severe periodontal disease is not associated with alterations in kidney functions.²⁷

CONCLUSIONS

In spite of great strides in the field of dentistry, oral health remains an issue which is not taken very seriously especially by under privileged groups in both developed and developing countries. Periodontal diseases

have always been considered one of the most important global oral health burdens.

CKD and its con-comitant sequences represent a major health problem globally. In the absence of a regular national registry data, the exact prevalence of CKD in India is not clear. According to WHO Global Burden of Disease Project, diseases of the kidney and urinary tract contribute to global burden with approximately 8,50,000 deaths every year and 115,010,107 disability adjusted life years.²⁸

In view of the current available data, World's/India's exploding population and considering the large populace living below poverty line, it definitely appears that the resources and skill for taking care of this large

case load, both in terms of personal and health care infrastructure do not currently exist in India and other developing countries. One of the ways to tackle this imposing problem is early diagnosis and taking preventive measures.

It is definitely very exciting to think that by controlling periodontal disease, treating it and thereby helping to preserve natural dentition, we could reduce the incidence and progression of CKD. It is time for the medical fraternity and dental surgeons to unite and literally fight tooth and nail against this disease that threatens the human population with an ever increasing number of death and disability cases.

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