

Systemic Consequences of Poor Oral Health in Chronic Kidney Disease Patients

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Summary

Changes in the oral cavity, such as periodontitis and other manifestations of poor oral health, are common in patients with chronic kidney disease (CKD) and may contribute to increased morbidity and mortality because of systemic consequences such as inflammation, infections, protein-energy wasting, and atherosclerotic complications. Poor oral health in CKD patients may thus represent an important, but often overlooked, problem. Several studies show that uremic patients have higher rates of decayed, missing, and filled teeth, loss of attachment, and periapical and mucosal lesions than the general population. The consequences of poor oral health may be more severe in CKD patients because of advanced age, common comorbidities such as diabetes, concurrent medications, and a state of immune dysfunction that may increase the risk for systemic consequences of periodontitis and other oral and dental pathologic conditions. Poor dentition and other signs of poor oral health should be an alarm clock also at early stages of CKD. However, it remains to be determined whether more successful management of poor oral health and periodontitis will reduce the risk of inflammation, infection, protein-energy wasting, and atherosclerotic complications in CKD patients. This review explores etiological factors and potential systemic consequences of poor oral health in CKD patients as well as possible preventive and therapeutic strategies.

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Introduction

Cardiovascular disease (CVD), which is often due to or combined with atherosclerosis and infectious complications, is the main cause of death in patients with chronic kidney disease (CKD) (1,2). A number of traditional, novel, and uremia-specific risk factors coexist in CKD and contribute to the increased cardiovascular risk in CKD population (1). Poor oral health, which is related to advanced age and diabetes mellitus, may constitute an under-recognized novel risk factor, because recent studies have shown how periodontitis associates with coronary heart disease and cerebrovascular disease in the general population (3) as well as in hemodialysis (HD) patients (4). A plausible explanation would involve bacterial pathogens causing periodontitis, leading to systemic inflammation as induced by lipopolysaccharide coats and thus triggering atherogenesis, thrombus formation, and platelet aggregation (5). However, periodontal diseases are treatable and modifiable risk factors (6,7). Furthermore, novel links between manifestations of poor oral health and systemic complications in CKD such as protein-energy wasting (PEW), infections, and atherosclerotic complications are being established (Figures 1 and 2). In this review, we explore these links and possible measures to tackle these problems.

Common Orofacial Problems in CKD Patients

As a consequence of a number of uremic metabolic, endocrinological, and immunological imbalances, CKD patients suffer from numerous systemic compli-

cations that may contribute to poor oral health (8). Although there are no specific signs in the oral cavity indicating the presence of CKD (9), a whole range of changes occur in the oral cavity that are associated with CKD itself or with the CKD therapy (10,11) (Figure 3). Indeed, CKD has been reported to affect the teeth (9,12–15), oral mucosa (10,16–20), bone (11,12,21–26), periodontium (27–30), salivary glands (17,31,32), tongue (10,33), mouth cavity (34–36), and temporomandibular joint (37).

Several studies have demonstrated higher rates of oral pathology in dialysis patients (16,17,27) with one or more oral symptoms (17,35,38) such as xerostomia, taste disturbances, uremic odor, tongue coating, mucosal inflammation, mucosal petechia/ecchymosis, oral ulceration, or enamel hypoplasia (16,36,39). Xerostomia (or dryness of the mouth) may predispose to caries and gingival inflammation as well as contribute to difficulties with speech, denture retention, mastication, dysphagia, sore mouth, loss of taste, and infections (40). CKD patients are also often prone to retrograde parotitis, which is believed to result from a combination of direct gland involvement, chemical inflammation, side effects of drug therapy, dehydration, and mouth breathing (34). Patients with renal failure often complain of an ammonia-like bad odor, perhaps because of the high urea content in saliva and its subsequent breakdown to ammonia. Increased dental calculus has been observed, perhaps as a consequence of a high salivary urea and phosphate levels. Interestingly, however, the antibacterial effect of

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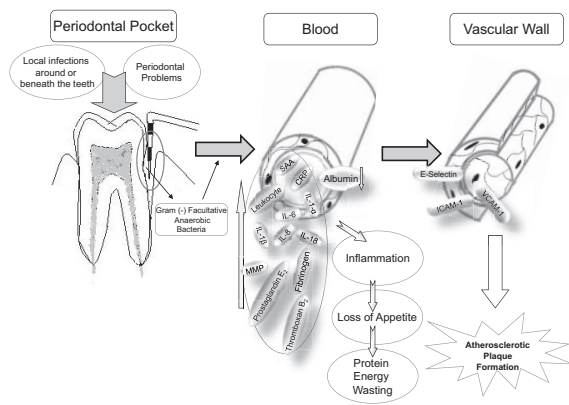


Figure 1. | Hypothetic model for how periodontitis may act as a potential cause of local and systemic inflammation in chronic kidney disease patients. SAA, serum amyloid A; CRP, C-reactive protein; MMP, matrix metalloproteinase.

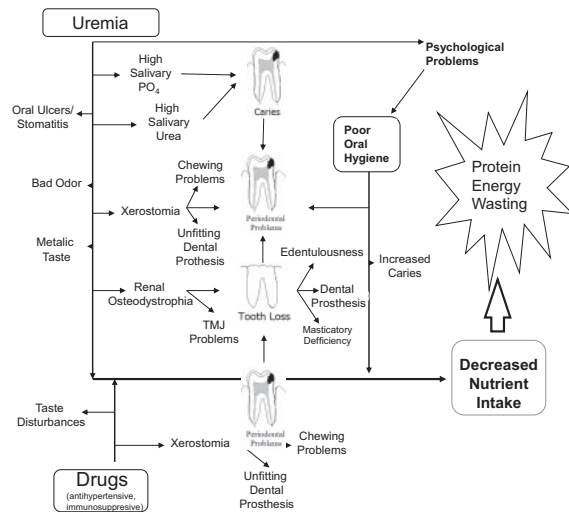


Figure 2. | Possible contribution of poor oral health in uremia to reduced nutrient intake and protein-energy wasting in chronic kidney disease patients.

urea may also be responsible for a lower caries rate as reported in HD patients (28,35). A spectrum of oral mucosal lesions, including white and erythematous patches and/or ulceration, lichen planus-like disease, oral hairy leukoplakia, histopathologically similar lesions to Epstein-Barr virus, macules, nodules, and non-Hodgkin’s lymphoma and/or Kaposi’s sarcoma, has been described in dialysis patients and in kidney transplant recipients secondary to both drug-related immunosuppression or an associated drug (17). The prevalence of cyclosporin-induced gingival hyperplasia in renal transplant patients varies from 22 to 58% in different reports and is more common in patients with increased cyclosporin dosage, in those with increased dental plaque and gingival inflammation, and in younger patients (41). The incidence of tacrolimus-induced gingival hyperplasia in renal transplant patients is lower, generally between 0 and 15% (41).

Although rare, uremic stomatitis is another clinical finding in advanced uremia; it consists of erythematous, ulcerative, hemorrhagic, and hyperkeratotic forms (42). The first two forms may occur as painful anterior mucosal lesions on the ventral tongue that usually heal spontaneously, after treatment of uremia (43). The hemorrhagic and hyperkeratotic forms may occur because of bleeding diathesis and long standing uremia, respectively (42). An intraoral form of “uremic frost” that can be observed in untreated uremia results from remaining urea crystals left on epithelial surfaces after saliva evaporation. Erosions of the dentition may occur because of regurgitation resulting from nausea (25). The manifestations of renal osteodystrophy in mandible, maxilla, and the oral cavity include demineralization, decreased trabeculation, loss of lamina dura, radiolucent giant cell lesions, macrognathia, metastatic soft-tissue calcifications, tooth mobility, malocclusion, enamel hypoplasia, and pulp stones (21,44,45).

Poor Oral Health as a Source of Inflammation

Gingivitis (defined as inflammation of the gingiva) and periodontitis (inflammation of the gingiva plus supporting tissues of the teeth) are common manifestations of poor oral health. Periodontitis represents a potential source of inflammation, and during the formation of periodontal pockets colonized with gram-negative anaerobic bacteria, an inflammatory cell infiltrate is recruited into the lesion that secretes proinflammatory mediators (41,46). Both gingivitis and periodontitis are seen more frequently in ESRD patients (47–49). Gingival hyperplasia is a relatively common periodontal complication in renal transplantation patients that has been attributed to cyclosporin dosage and the presence of dental plaques, likely contributing to gingival inflammation (50). Estimates of the prevalence of periodontitis vary across studies (Table 1): a 14% prevalence of moderate to severe periodontitis was reported among individuals >20 years of age in the United States population (51) and 13% of subjects had severe periodontitis in a normal Swedish population (52). This divergency in prevalence depends on methodological, etiological, age-related, racial, ethnic, socioeconomic, cultural, and behavioral factors that may be specific for each country. To exemplify this, although a Spanish report (27) showed significant higher plaque and calculus indices and lower salivary secretions in HD patients as compared with healthy controls, a report from The Netherlands (37) described comparable levels for most dental aspects. Undoubtedly, cross-cultural studies are needed on this neglected issue of dental problems in patients with ESRD. For comparative analyses it would be desirable to follow World Health Organization recommendations for a systematic classification on the basis of the severity of different aspects of periodontal disease including gingival index, papillary bleeding index plaque index, and clinical attachment level (53).

The causes of increased periodontitis are not fully

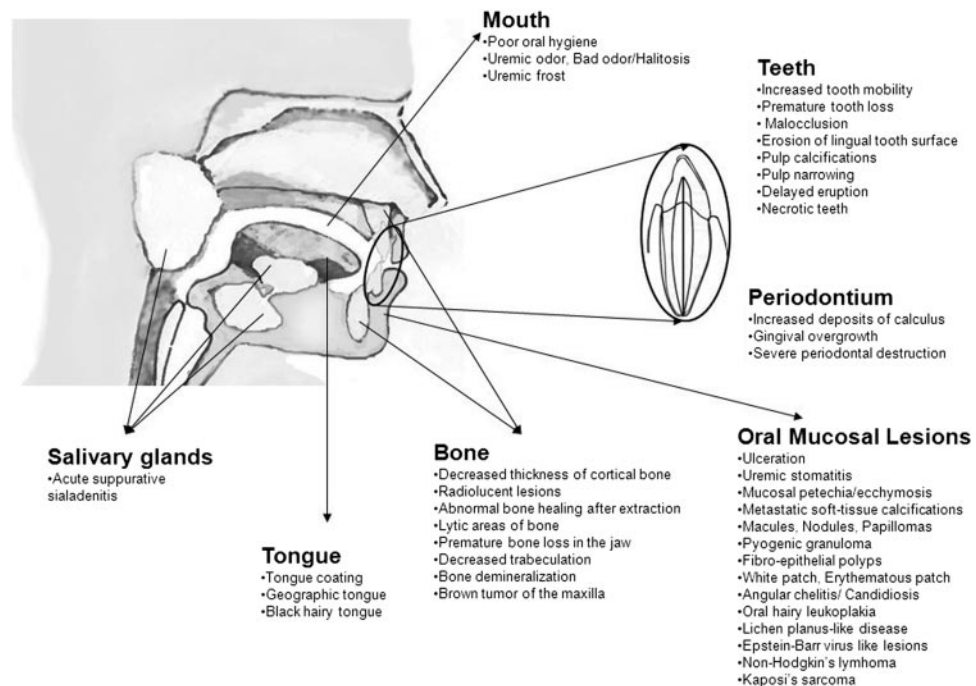


Figure 3. | Common orofacial problems associated with chronic kidney disease itself or caused by therapy.

Study	Country	Treatment and Vintage	Sample Size	Mean Age (Years)	DM (%)	Periodontitis (%)	Gingivitis (%)
Naugle <i>et al.</i> (16)	USA	HD 1 to 3 years	45			28	36
Klassen and Krasko (11)	Canada	HD 25 ± 30 months	94	51.1 ± 18.8	33		99
Al-Wahadni and Al-Omari (49)	Jordan	HD 1 to 3 years	47	42.9 ± 12.5	NA	29.8 ^b	100
Chen <i>et al.</i> (48)	Taiwan	HD 49 ± 3 months	253	58.8 ± 0.8	39.5	58.9 ^c	
Kshirsagar <i>et al.</i> (46)	USA	HD 4 years	154	54.6 ± 13.3	22	23	
Buhlin <i>et al.</i> (47)	Sweden	Predialysis ^a	51	55.9	27.5	36 ^d	46
Cengiz <i>et al.</i> (82)	Turkey	PD	110	44.3 ± 0.6	NA	67.3 ^c	

DM, diabetes mellitus; NA, not applicable.
^aClose to starting dialysis.
^bModerate periodontal disease.
^cModerate to severe periodontitis.
^dSevere periodontitis.

elucidated, but it has been proposed that repeated systemic anticoagulation may predispose HD patients to gingival bleeding and facilitate bacterial colonization (53). At the same time, oral barriers might have deteriorated because of disturbed humoral defense (46). Commencement of dialysis therapy appears to be accompanied by major changes in the oral condition (46), and therefore periodontal disease has been reported to progress in severity across predialysis,

peritoneal dialysis (PD) and HD patients, respectively (53). Unfortunately, very few studies compared the prevalence of these symptoms between HD and PD patients. One study, however, reports periodontitis to be less severe in PD patients—and moderate in predialysis CKD patients—as compared with HD patients (53). Transplant patients were reported to have less halitosis when compared with HD, PD, and predialysis patients, leading to the hypothesis that spe-

cific uremic toxins may determine halitosis in the CKD population (8). Additionally, renal transplantation also enhances salivary flow and decreases symptoms of xerostomia and thirst (54).

Several possible reasons have been proposed to account for the poor oral health in uremia that has been associated with immune dysfunction including defects in lymphocyte and monocyte function (41). Altered cellular immunity along with malnutrition contributes to a immunodeficient state in uremia. Uremic patients are more prone to bacterial infections because of malnutrition, which leads to a diminished ability to produce antibodies (35). In support of this, increased gingival inflammation has been reported in association with longer dialysis vintage (48), although this finding could not be observed in a more recent study (4). Because a strong association exists in the general population between diabetes and periodontitis (55), it has been proposed that the increased prevalence of diabetes in ESRD could also contribute to the over-representation of periodontitis (41). Psychological factors and depressive symptoms may decrease the priority of maintaining good oral health in ESRD population (11,16,41). Finally, secondary hyperparathyroidism has been suggested as a possible cause of periodontal disease in ESRD patients, but this has not been confirmed in recent exploratory analyses (56).

A proposed model for how periodontitis could act as a potential cause of local and systemic inflammation in CKD patients is shown in Figure 1. At least two reports support the hypothesis that periodontitis may contribute to the systemic inflammatory burden in the ESRD population (48,57). Poor oral health status was found in 80% of 253 HD patients with periodontal disease and was associated with both high C-reactive protein and low serum albumin levels in univariate analysis but not in multivariate (48). On the basis of these findings, it is important to monitor and maintain the oral health status of patients undergoing dialysis, as well as in patients who are considered as potential renal transplant candidates. When a patient is considered for renal transplantation, ensuring healthy dentition becomes important because of the use of immunosuppressive drugs, which may further predispose to oral and possibly disseminated infection (11). Although a number of studies suggest that the oral hygiene status of ESRD patients may be worse than in the general population, only very few assessed the frequency of tooth brushing, flossing, and dental visits in these patients: tooth brushing was reported to be done once or more daily in 79% of the patients, less than once daily in 14% and never in 7% of the patients (11). The last dental visit(s) was reported as <1 year ago, 1 to 2 years ago, 2 to 5 years ago, and >5 years ago in 37, 20, 7, and 35%, respectively, among dentated dialysis patients. Another study reported tooth brushing frequencies as twice a day, once a day, irregular, and never in 14, 29, 40, and 17% of the patients, respectively (58).

In a study comprising 86 dentated HD patients in whom sera were assayed for IgG-antibody levels to

six periodontal species, the IgG antibody levels to *Porphyromonas gingivalis* were elevated in patients with systemic inflammation (57), leading the authors to propose such antibodies as a serum marker of destructive periodontal disease. Elevation of salivary macrophage inflammatory protein-1 α , a chemokine that recruits osteoclast progenitors, was suggested as a biomarker of early events in inflammatory-induced periodontal bone loss that precedes radiographic evidence in carriers of *Aggregatibacter actinomycetemcomitans*, an oral commensal that can cause severe infections in the periodontium (59).

Poor Oral Health as a Contributor to Infectious Diseases

Periodontitis represents a potential source of episodes of bacteremia, especially in the immunocompromised patient. This may not be surprising considering that the overall size of periodontal lesions may range from 1500 to 2000 mm² (60) and that the number of bacteria can exceed 1×10^8 in a single periodontal pocket (61). Although bacteremia can occur after almost any type of dental manipulations including tooth brushing and flossing, these episodes are, however, usually transient and inconsequential for healthy individuals. In contrast, bacteremia in patients with dental caries and periodontal disease tends to be more sustained, raising the risk of hematogenous dissemination of the dental infection (62). Bacteria can adhere to damaged heart valves and cause endocarditis, and for this reason prophylactic antibiotics are recommended in patients with valvular heart disease (62). It is possible that the immune dysfunction in uremia (2) may substantially increase the risk for such systemic consequences of periodontitis and other oral pathologic conditions because we cannot fully explain why these patients suffer from such high rates of inflammation, infection, and CVD. Although links between oral health and infections have not been systematically studied, there are several reports in the literature. Bacteria from oral biofilms may be aspirated into the respiratory tract and may cause the initiation and progression of systemic infectious conditions such as pneumonia in high-risk subjects (63). A recent Swedish study showed that 32% of ESRD patients and 11% of healthy controls had fungal hyphae through microscopy on buccal smears (64). Clinical signs, including oral lesions associated with fungal infection, membranous candidiasis, erythematous oral stomatitis, and angular cheilitis were found in 15% of the ESRD patients but not in the control group. Patients and controls with self-experienced mouth dryness were both likely to have fungal hyphae. Fungal colonization in the oral mucosal membranes may therefore have potential consequences like sepsis.

Poor Oral Health as a Contributor to Atherosclerotic Complications

In response to an infectious and inflammatory trigger, nonspecific innate and more specific adaptive

immune responses occur (65). The innate immune system provides immediate protection against infection and inflammation by recruiting of immune cells, activation of complement systems, identification and removal of foreign substances, and activation of the adaptive immune system (66). However, in inflammatory diseases, the responses become chronic, and chronic diseases may develop because of repeated unchecked and maladapted inflammatory responses over the years (65). The earliest changes in atherosclerosis occur in the endothelium, leading to accumulation of monocytes and T cells, migration of polymorphonuclear leukocytes into the intima, differentiation and proliferation of the monocytes, and eventually development of fibrous cap. To examine the role of chronic bacterial infections as risk factors for atherosclerotic complications, the association between poor dental health and acute myocardial infarction was investigated in two separate case-control studies of a total of 100 patients with acute myocardial infarction and 102 controls (67). Dental health was found to be significantly worse in patients with acute myocardial infarction than in controls and the association remained valid after adjustment for age, social class, smoking, serum lipid concentrations, and the presence of diabetes (67). Poor oral hygiene, determined by the extent of dental debris and calculus, was associated with an increased incidence of coronary heart disease, and in men younger than 50 years at baseline, periodontal disease was a risk factor for coronary heart disease (68). Because periodontal disease and poor oral hygiene are associated with total mortality, assessments of dental health may be of value as a general indicator of personal hygiene and possibly health care practices (68). Patients with periodontitis exhibited dyslipidemia and increased nonfasting serum glucose levels compared with controls, suggesting a possible link between periodontitis, systemic inflammation, and a dysmetabolic state in otherwise healthy individuals (69).

Thus, in periodontitis, overgrowth of gram-negative bacteria may cause endotoxemia and systemic inflammation leading to CVD (70). Periodontal disease may represent a risk factor for atherosclerosis and thromboembolic events (71). Periodontal treatment could reduce the risk of coronary heart disease and therefore become one of the preventing strategies (72).

Poor Oral Health as a Contributor to Protein-Energy Wasting

Oral diseases contribute to the elevated incidence of PEW in CKD patients (73), and proposed mechanistic links are summarized in Figure 2. All of these risk factors are interrelated in a vicious circle: whereas poor oral health may lead to both inflammation and PEW in CKD patients, numerous pathways associate the accumulation of proinflammatory cytokines with different aspects of PEW, including anorexia, muscle loss, low anabolic hormones, increased energy expenditure, and insulin resistance (74–76).

Dryness, pain, or a bad taste in the mouth may lead to anorexia and nutrient deficiencies (77–79). Studies in the general population suggest that edentulous subjects are prone to have an inappropriate dietary intake (such as ingesting too little protein and too much calorie-rich, high-fat food) as compared with dentate persons. Whereas the number of teeth is of importance for masticatory function, having premolar and molar teeth (which help to occlude) is especially important for nutritional status. The increased periodontitis and dental caries rates of CKD patients lead to tooth loss, which may result in chewing difficulties because of inadequate occlusive surfaces or the limitations of prostheses (80).

Noncarious tooth tissue loss is more prevalent in CKD individuals than in the general population (25). This was suggested by some authors as a possible consequence of secondary hyperparathyroidism leading to increased tooth mobility caused by excessive resorption of alveolar bone (14). However, this finding could not be confirmed in a more recent study (56). Severe hyperparathyroidism has been reported to alter the size and shape of the jawbone, which fails to return to normal contours even after parathyroidectomy (44). An association between the severity of renal dysfunction and the formation of dental calculus—an additional manifestation of disturbed calcium-phosphorus homeostasis—was reported in pediatric CKD patients in the predialysis stage, undergoing dialysis, or after kidney transplantation with healthy children as controls (81). The most abundant amount of calculus and the highest salivary urea level were found in the dialyzed children. These patients had the highest oral mucosal pH levels, most likely because of the abundant supply of urea from the salivary gland secretion, which after hydrolysis by bacteria leads to release of ammonia and elevation of pH in the dental plaque, further promoting calcium and phosphorus precipitation (81). Thus, retention of urea may facilitate dental plaque alkalization, thereby contributing to a higher rate of calculus formation in dialyzed patients. In addition, the lowest salivary magnesium concentration was found in dialysis patients, and because magnesium may inhibit the calcification process, this may further explain the amplification of dental calculus formation in the dialyzed patients. Finally, this study showed that oxalate, which is retained in uremia, was a significant component of dental calculus in the dialyzed patients.

Severe periodontitis and poor dental status were associated with low serum albumin levels and PEW in both HD and PD adult patients (46,82). A latter study in HD patients described signs of poor oral health status in 80% of the patients who often had severe periodontitis associated with both poor nutritional status and systemic inflammation (48).

Certain medications like antidepressants, antipsychotics, antiemetics, and antihistamines can reduce salivary flow, creating the condition known as xerostomia. The risk for xerostomia increases with the number of drugs being taken and with increasing age

(83). Because saliva lubricates and protects soft and hard oral tissues, helps soften foods, and facilitates swallowing (84), reduced salivary flow likely contributes to thirst and deglutition problems, which may ultimately affect both satiety by water distension in the bowels and diminished nutrient intake in CKD patients. Table 2 summarizes medications that may potentially cause xerostomia (84,85). Of note, oral dryness and thirst decrease whereas salivary flow rates increase after renal transplantation (54).

Approximately 30% of patients with advanced CKD are reported to have a “bad” or a “metallic” taste in their mouths, which has been associated with metabolic changes, diverse drugs, a reduced number of taste buds, and changes in both salivary flow rate and composition (36,54,86). Altered palatability issues

may indeed modify the patient’s perception of foods and influence choice. The severity of PEW in ESRD patients can also be aggravated by temporomandibular joint complaints, which are also relatively common in dialysis patients (37), perhaps as a consequence of renal osteodystrophy. Finally, an intervention program including oral cavity check-ups and education on oral health was associated with an improvement in the patient’s nutritional status (87).

Proposed Measures to Prevent and Treat Poor Oral Health in CKD Patients

The above-discussed sections describe several compelling reasons why it is important to improve oral health in the CKD population. Namely, poor oral health in CKD patients relates to PEW and inflammation (46,48,82,87), and moderate-to-severe periodontal disease predisposes to CVD-related mortality five-fold (4).

The higher prevalence of calculus in CKD patients may indicate insufficient oral care (37,88). Tooth brushing, flossing, and mouthwashes may reduce gingivitis (61), and oral hygiene measures, mechanical debridement, and/or surgery can effectively prevent the initiation and progression of periodontal diseases (89) (Figure 4). To reduce the risks of probing of

Categories	Subgroups
Antihypertensive agents	β -Adrenergic blocking agents Diuretics α -Adrenergic blocking agents
Psychotropic medications	Antidepressants Anxiolytics/ anticonvulsants Tricyclic antidepressants Tetracyclic antidepressants Serotonin reuptake inhibitors Narcotic analgesics
Anticholinergics and related drugs	Antispasmodics
Sympathetic agonists	Anticholinergics Histamine H ₂ antagonist Antiemetic/antivertigo agents Bronchodilators Corticosteroids Anti-Parkinson/ dopamine receptor agonists

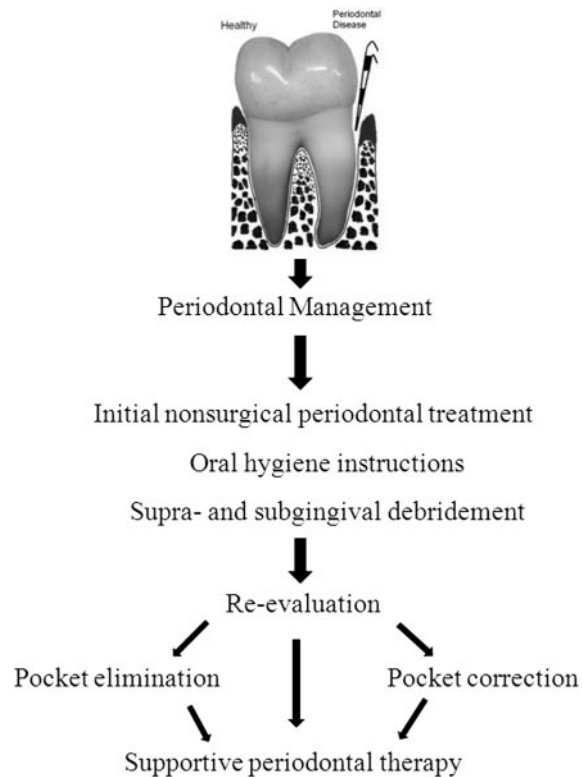


Figure 4. | Suggested schedule for interventions and follow-up of periodontitis in chronic kidney disease patients. The periodontitis treatment should be carried out as short treatment sessions on a dialysis-free day in hemodialysis patients. Note that antibiotic prophylaxis is necessary in transplant patients and is recommended in hemodialysis patients. Modified from Claffey et al. (89).

periodontal pockets, prophylaxis with antibiotics should be considered (46). Prevention and treatment should aim at controlling the dental plaques and other risk factors, arresting progressive disease, and restoring lost tooth support with correction or replacement of defective prostheses (61). To maximize the effect of the periodontal treatment, patients should be encouraged to stop smoking. Advice to reduce the severity of xerostomia may include: avoiding mouth breathing; using a humidifier; avoiding tobacco, caffeine, alcohol, and mouthwashes containing alcohol; using sugar-free chewing gum to stimulate salivary flow; using saliva substitutes; and, if possible, modifying dosage of or changing xerostomic medications (83,90).

ESRD patients have a complicated medical condition of which their dentists need to be aware; for example, patients may need antibiotic prophylaxis; local anesthetics with reduced epinephrine, especially in patients with hypertension; and withholding of anticoagulants/antiplatelet agents in conjunction with the dental procedure (11). There have been reports on the spread of hepatitis C in dialysis patients by dental surgery, suggesting oral instrumentation as a possible route of viral disease transmission (91). Therefore, careful surveillance in dental care is important in dialysis patients including awareness of a patient's viral status before oral instrumentation.

Conclusions

Oral health is often poor in CKD patients and may contribute to PEW, inflammation, infections, and atherosclerotic complications, all of them important problems that would justify an increased attention to dental care and a better awareness in the clinic. Maintaining a healthy and functional dentition in CKD patients has an additional complementary role that most likely exceeds benefits seen in the general population. Poor dentition should be an alarm clock even at very early stages of CKD, in dialysis patients, and in patients undergoing kidney transplantation. Finally, unsatisfactory daily oral hygiene habits and insufficient awareness of the importance of oral health apparently warrants the common effort of both dentists and nephrologists.

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Disclosures

Bengt Lindholm is employed by Baxter Healthcare. Peter Stenvinkel is a member of the scientific advisory board of Gambro AB. None of the other authors have any conflicts of interest to declare.

References

1. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy Z: Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: How do new pieces fit into the uremic puzzle? *Clin J Am Soc Nephrol* 3: 505–521, 2008
2. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, Tranaeus A, Stenvinkel P, Lindholm B: Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 3: 1526–1533, 2008
3. Grau AJ, Buggle F, Ziegler C, Schwarz W, Meuser J, Tasman AJ, Buhler A, Benesch C, Becher H, Hacke W: Association between acute cerebrovascular ischemia and chronic and recurrent infection. *Stroke* 28: 1724–1729, 1997
4. 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* 75: 746–751, 2009
5. Beck JD, Offenbacher S, Williams R, Gibbs P, Garcia R: Periodontitis: A risk factor for coronary heart disease? *Ann Periodontol* 3: 127–141, 1998
6. Craig RG, Kotanko P, Kamer AR, Levin NW: Periodontal diseases: A modifiable source of systemic inflammation for the end-stage renal disease patient on haemodialysis therapy? *Nephrol Dial Transplant* 22: 312–315, 2007
7. Craig RG, Spittle MA, Levin NW: Importance of periodontal disease in the kidney patient. *Blood Purif* 20: 113–119, 2002
8. Souza CM, Braosi AP, Luczyszyn SM, Casagrande RW, Pecoits-Filho R, Riella MC, Ignacio SA, Trevilatto PC: Oral health in Brazilian patients with chronic renal disease. *Rev Med Chil* 136: 741–746, 2008
9. Vesterinen M, Ruokonen H, Leivo T, Honkanen AM, Honkanen E, Kari K, Lindqvist C, Meurman JH: Oral health and dental treatment of patients with renal disease. *Quintessence Int* 38: 211–219, 2007
10. Summers SA, Tilakaratne WM, Fortune F, Ashman N: Renal disease and the mouth. *Am J Med* 120: 568–573, 2007
11. Klassen JT, Krasko BM: The dental health status of dialysis patients. *J Can Dent Assoc* 68: 34–38, 2002
12. Locsey L, Alberth M, Mauks G: Dental management of chronic haemodialysis patients. *Int Urol Nephrol* 18: 211–213, 1986
13. Galili D, Berger E, Kaufman E: Pulp narrowing in renal end stage and transplanted patients. *J Endod* 17: 442–443, 1991
14. Carmichael DT, Williams CA, Aller MS: Renal dysplasia with secondary hyperparathyroidism and loose teeth in a young dog. *J Vet Dent* 12: 143–146, 1995
15. Potter JL, Wilson NH: A dental survey of renal dialysis patients. *Public Health* 93: 153–156, 1979
16. Naugle K, Darby ML, Bauman DB, Lineberger LT, Powers R: The oral health status of individuals on renal dialysis. *Ann Periodontol* 3: 197–205, 1998
17. Proctor R, Kumar N, Stein A, Moles D, Porter S: Oral and dental aspects of chronic renal failure. *J Dent Res* 84: 199–208, 2005
18. King GN, Fullinlaw R, Higgins TJ, Walker RG, Francis DM, Wiesenfeld D: Gingival hyperplasia in renal allograft recipients receiving cyclosporin-A and calcium antagonists. *J Clin Periodontol* 20: 286–293, 1993
19. King GN, Healy CM, Glover MT, Kwan JT, Williams DM, Leigh IM, Thornhill MH: Prevalence and risk factors associated with leukoplakia, hairy leukoplakia, erythematous candidiasis, and gingival hyperplasia in renal transplant recipients. *Oral Surg Oral Med Oral Pathol* 78: 718–726, 1994
20. Chau NY, Reade PC, Rich AM, Hay KD: Allopurinol-

- amplified lichenoid reactions of the oral mucosa. *Oral Surg Oral Med Oral Pathol* 58: 397–400, 1984
21. Carl W: Chronic renal disease and hyperparathyroidism: Dental manifestations and management. *Compendium* 8: 697–704, 1987
 22. Michiwaki Y, Michi K, Yamaguchi A: Marked enlargement of the jaws in secondary hyperparathyroidism: A case report. *Int J Oral Maxillofac Surg* 25: 54–56, 1996
 23. Ganibegovic M: Dental radiographic changes in chronic renal disease. *Med Arh* 54: 115–118, 2000
 24. Okada H, Davies JE, Yamamoto H: Brown tumor of the maxilla in a patient with secondary hyperparathyroidism: A case study involving immunohistochemistry and electron microscopy. *J Oral Maxillofac Surg* 58: 233–238, 2000
 25. Levy HM: Dental considerations for the patient receiving dialysis for renal failure. *Spec Care Dentist* 8: 34–36, 1988
 26. Sampson E, Meister F Jr.: Dental complications in the end stage of renal disease. *Gen Dent* 32: 297–299, 1984
 27. Gavalda C, Bagan J, Scully C, Silvestre F, Milian M, Jimenez Y: Renal hemodialysis patients: Oral, salivary, dental and periodontal findings in 105 adult cases. *Oral Dis* 5: 299–302, 1999
 28. Epstein SR, Mandel I, Scopp IW: Salivary composition and calculus formation in patients undergoing hemodialysis. *J Periodontol* 51: 336–338, 1980
 29. Jaffe EC, Roberts GJ, Chantler C, Carter JE: Dental findings in chronic renal failure. *Br Dent J* 160: 18–20, 1986
 30. Thomason JM, Seymour RA, Rice N: The prevalence and severity of cyclosporin and nifedipine-induced gingival overgrowth. *J Clin Periodontol* 20: 37–40, 1993
 31. Bayraktar G, Kazancioglu R, Bozakioglu S, Yildiz A, Ark E: Evaluation of salivary parameters and dental status in adult hemodialysis patients. *Clin Nephrol* 62: 380–383, 2004
 32. Kao CH, Hsieh JF, Tsai SC, Ho YJ, Chang HR: Decreased salivary function in patients with end-stage renal disease requiring hemodialysis. *Am J Kidney Dis* 36: 1110–1114, 2000
 33. Hirshberg A, Kaplan I, Gorsky M: Beta-2-microglobulin-associated nodular amyloidosis of the tongue. *Int J Oral Maxillofac Surg* 27: 226–228, 1998
 34. Eigner TL, Jastak JT, Bennett WM: Achieving oral health in patients with renal failure and renal transplants. *J Am Dent Assoc* 113: 612–616, 1986
 35. De Rossi SS, Glick M: Dental considerations for the patient with renal disease receiving hemodialysis. *J Am Dent Assoc* 127: 211–219, 1996
 36. Kho HS, Lee SW, Chung SC, Kim YK: Oral manifestations and salivary flow rate, pH, and buffer capacity in patients with end-stage renal disease undergoing hemodialysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 88: 316–319, 1999
 37. Bots CP, Poorterman JH, Brand HS, Kalsbeek H, van Amerongen BM, Veerman EC, Nieuw Amerongen AV: The oral health status of dentate patients with chronic renal failure undergoing dialysis therapy. *Oral Dis* 12: 176–180, 2006
 38. Phelps KR, Bansal M, Twersky J: Jaw enlargement complicating secondary hyperparathyroidism in three hemodialysis patients. *Clin Nephrol* 41: 173–179, 1994
 39. Jaspers MT: Unusual oral lesions in a uremic patient: Review of the literature and report of a case. *Oral Surg Oral Med Oral Pathol* 39: 934–944, 1975
 40. Porter SR, Scully C, Hegarty AM: An update of the etiology and management of xerostomia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 97: 28–46, 2004
 41. Craig RG: Interactions between chronic renal disease and periodontal disease. *Oral Dis* 14: 1–7, 2008
 42. Antoniadis DZ, Markopoulos AK, Andreadis D, Balaskas I, Patrikalou E, Grekas D: Ulcerative uremic stomatitis associated with untreated chronic renal failure: Report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 101: 608–613, 2006
 43. Hovinga J, Roodvoets AP, Gaillard J: Some findings in patients with uraemic stomatitis. *J Maxillofac Surg* 3: 125–127, 1975
 44. Hata T, Irei I, Tanaka K, Nagatsuka H, Hosoda M: Macrognathia secondary to dialysis-related renal osteodystrophy treated successfully by parathyroidectomy. *Int J Oral Maxillofac Surg* 35: 378–382, 2006
 45. Molpus WM, Pritchard RS, Walker CW, Fitzrandolph RL: The radiographic spectrum of renal osteodystrophy. *Am Fam Physician* 43: 151–158, 1991
 46. Kshirsagar AV, Craig RG, Beck JD, Moss K, Offenbacher S, Kotanko P, Yoshino M, Levin NW, Yip JK, Almas K, Lupovici E, Falk RJ: Severe periodontitis is associated with low serum albumin among patients on maintenance hemodialysis therapy. *Clin J Am Soc Nephrol* 2: 239–244, 2007
 47. Buhlin K, Barany P, Heimburger O, Stenvinkel P, Gustafsson A: Oral health and pro-inflammatory status in end-stage renal disease patients. *Oral Health Prev Dent* 5: 235–244, 2007
 48. Chen LP, Chiang CK, Chan CP, Hung KY, Huang CS: Does periodontitis reflect inflammation and malnutrition status in hemodialysis patients? *Am J Kidney Dis* 47: 815–822, 2006
 49. Al-Wahadni A, Al-Omari MA: Dental diseases in a Jordanian population on renal dialysis. *Quintessence Int* 34: 343–347, 2003
 50. Ellis JS, Seymour RA, Taylor JJ, Thomason JM: Prevalence of gingival overgrowth in transplant patients immunosuppressed with tacrolimus. *J Clin Periodontol* 31: 126–131, 2004
 51. Oliver RC, Brown LJ, Loe H: Periodontal diseases in the United States population. *J Periodontol* 69: 269–278, 1998
 52. Hugoson A, Norderyd O, Slotte C, Thorstensson H: Distribution of periodontal disease in a Swedish adult population 1973, 1983 and 1993. *J Clin Periodontol* 25: 542–548, 1998
 53. Borawski J, Wilczynska-Borawska M, Stokowska W, Mysliwiec M: The periodontal status of pre-dialysis chronic kidney disease and maintenance dialysis patients. *Nephrol Dial Transplant* 22: 457–464, 2007
 54. Bots CP, Brand HS, Poorterman JH, van Amerongen BM, Valentijn-Benz M, Veerman EC, ter Wee PM, Nieuw Amerongen AV: Oral and salivary changes in patients with end stage renal disease (ESRD): A two year follow-up study. *Br Dent J* 202: E3, 2007
 55. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, Norderyd OM, Genco RJ: Assessment of risk for periodontal disease: I. Risk indicators for attachment loss. *J Periodontol* 65: 260–267, 1994
 56. Frankenthal S, Nakhoul F, Machtei EE, Green J, Ardekian L, Laufer D, Peled M: The effect of secondary hyperparathyroidism and hemodialysis therapy on alveolar bone and periodontium. *J Clin Periodontol* 29: 479–483, 2002
 57. Rahmati MA, Craig RG, Homel P, Kaysen GA, Levin NW: Serum markers of periodontal disease status and inflammation in hemodialysis patients. *Am J Kidney Dis* 40: 983–989, 2002
 58. Gurkan A, Kose T, Atilla G: Oral health status and oral hygiene habits of an adult Turkish population on dialysis. *Oral Health Prev Dent* 6: 37–43, 2008
 59. Fine DH, Markowitz K, Furgang D, Fairlie K, Ferrandiz J, Nasri C, McKiernan M, Donnelly R, Gunsolley J: Macrophage inflammatory protein-1alpha: A salivary biomarker of bone loss in a longitudinal cohort study of children at risk for aggressive periodontal disease? *J Periodontol* 80: 106–113, 2009
 60. Loos BG: Systemic effects of periodontitis. *Ann R Australas Coll Dent Surg* 18: 27–29, 2006

61. Pihlstrom BL, Michalowicz BS, Johnson NW: Periodontal diseases. *Lancet* 366: 1809–1820, 2005
62. Mattar CS, Keith RL, Byrd RP, Jr., Roy TM: Septic pulmonary emboli due to periodontal disease. *Respir Med* 100: 1470–1474, 2006
63. Paju S, Scannapieco FA: Oral biofilms, periodontitis, and pulmonary infections. *Oral Dis* 13: 508–512, 2007
64. Thorman R, Neovius M, Hylander B: Prevalence and early detection of oral fungal infection: A cross-sectional controlled study in a group of Swedish end-stage renal disease patients. *Scand J Urol Nephrol* 1–6, 2009
65. Van Dyke TE, Kornman KS: Inflammation and factors that may regulate inflammatory response. *J Periodontol* 79: 1503–1507, 2008
66. Medzhitov R, Janeway, C.: Jr.: Innate immunity. *N Engl J Med* 343: 338–344, 2000
67. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesaniemi YA, Syrjala SL, Jungell PS, Isoluoma M, Hietaniemi K, Jokinen MJ: Association between dental health and acute myocardial infarction. *BMJ* 298: 779–781, 1989
68. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM: Dental disease and risk of coronary heart disease and mortality. *BMJ* 306: 688–691, 1993
69. Nibali L, D’Aiuto F, Griffiths G, Patel K, Suvaran J, Tonetti MS: Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: A case-control study. *J Clin Periodontol* 34: 931–937, 2007
70. Pussinen PJ, Tuomisto K, Jousilahti P, Havulinna AS, Sundvall J, Salomaa V: Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. *Arterioscler Thromb Vasc Biol* 27: 1433–1439, 2007
71. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S: Periodontal disease and cardiovascular disease. *J Periodontol* 67: 1123–1137, 1996
72. Ouyang XY: Association between periodontal disease and coronary heart disease. *Beijing Da Xue Xue Bao* 40: 112–115, 2008
73. Rhodus NL: Oral health and systemic health. *Minn Med* 88: 46–48, 2005
74. Carrero JJ, Qureshi AR, Parini P, Arver S, Lindholm B, Barany P, Heimbürger O, Stenvinkel P: Low serum testosterone increases mortality risk among male dialysis patients. *J Am Soc Nephrol* 20: 613–620, 2009
75. Carrero JJ, Chmielewski M, Axelsson J, Snaedal S, Heimbürger O, Barany P, Suliman ME, Lindholm B, Stenvinkel P, Qureshi AR: Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr* 27: 557–564, 2008
76. Carrero JJ, Qureshi AR, Axelsson J, Avesani CM, Suliman ME, Kato S, Barany P, Snaedal-Jonsdottir S, Alvestrand A, Heimbürger O, Lindholm B, Stenvinkel P: Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite. *Am J Clin Nutr* 85: 695–701, 2007
77. Carrero JJ: Identification of patients with eating disorders: Clinical and biochemical signs of appetite loss in dialysis patients. *J Ren Nutr* 19: 10–15, 2009
78. Carrero JJ, Aguilera A, Stenvinkel P, Gil F, Selgas R, Lindholm B: Appetite disorders in uremia. *J Ren Nutr* 18: 107–113, 2008
79. Ritchie CS, Joshipura K, Hung HC, Douglass CW: Nutrition as a mediator in the relation between oral and systemic disease: Associations between specific measures of adult oral health and nutrition outcomes. *Crit Rev Oral Biol Med* 13: 291–300, 2002
80. Sheiham A, Steele JG, Marceles W, Finch S, Walls AW: The relationship between oral health status and Body Mass Index among older people: A national survey of older people in Great Britain. *Br Dent J* 192: 703–706, 2002
81. Davidovich E, Davidovits M, Peretz B, Shapira J, Aframian DJ: The correlation between dental calculus and disturbed mineral metabolism in pediatric patients with chronic kidney disease. *Nephrol Dial Transplant* 2009
82. Cengiz MI, Bal S, Gokcay S, Cengiz K: Does periodontal disease reflect atherosclerosis in continuous ambulatory peritoneal dialysis patients? *J Periodontol* 78: 1926–1934, 2007
83. Guggenheimer J, Moore PA: Xerostomia: etiology, recognition and treatment. *J Am Dent Assoc* 134: 61–69; quiz 118–119, 2003
84. Janket SJ, Jones J, Rich S, Miller D, Wehler CJ, Van Dyke TE, Garcia R, Meurman JH: The effects of xerogenic medications on oral mucosa among the Veterans Dental Study participants. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 103: 223–230, 2007
85. Loesche WJ, Bromberg J, Terpenning MS, Bretz WA, Dominguez BL, Grossman NS, Langmore SE: Xerostomia, xerogenic medications and food avoidances in selected geriatric groups. *J Am Geriatr Soc* 43: 401–407, 1995
86. Bots CP, Brand HS, Veerman EC, Valentijn-Benz M, Van Amerongen BM, Valentijn RM, Vos PF, Bijlsma JA, Bezemer PD, Ter Wee PM, Amerongen AV: Interdialytic weight gain in patients on hemodialysis is associated with dry mouth and thirst. *Kidney Int* 66: 1662–1668, 2004
87. Hopper L, Cole M: Risk factors affecting nutritional status of dialysis patients: A quality improvement project. *Nephrol News Issues* 22: 26–34, 2008
88. Atassi F: Oral home care and the reasons for seeking dental care by individuals on renal dialysis. *J Contemp Dent Pract* 3: 31–41, 2002
89. Claffey N, Polyzois I, Ziaka P: An overview of nonsurgical and surgical therapy. *Periodontol* 2000 36: 35–44, 2004
90. Dawes C: How much saliva is enough for avoidance of xerostomia? *Caries Res* 38: 236–240, 2004
91. Vagelli G, Calabrese G, Pratesi G, Gonella M: Non A-non B hepatitis in a dialysis population: Spread by dental surgery? *Clin Nephrol* 22: 268, 1984