REVIEW

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The oral cavity as a diagnostic interface in kidney disease: clinical markers and pathophysiological correlates - a systematic review.

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Abstract
Introduction. Chronic kidney disease (CKD) is not just an isolated renal disorder, but also a complex systemic condition with consequences that extend far beyond renal function alone. Among these, oral changes have become increasingly relevant because the oral cavity may reflect inflammatory, metabolic, microbiological and immunological alterations associated with kidney disease. Aim of the study. The aim of this systematic review was to evaluate the oral status of patients with chronic kidney disease by analyzing the main oral clinical manifestations and the principal pathophysiological mechanisms linking oral findings with CKD. Methods. A systematic review with narrative synthesis was performed to assess oral manifestations, salivary changes, periodontal involvement, oral microbiological findings, tongue-related features and salivary biomarkers in patients with chronic kidney disease. Results. The reviewed evidence consistently showed that patients with CKD present xerostomia, oral mucosal changes, taste disturbances, burning mouth sensation, gingival inflammation, periodontal disease, increased calculus accumulation, and salivary abnormalities. Several studies also suggested that saliva, periodontal status, and specific tongue-related findings may provide useful non-invasive information about kidney disease and, in some particular cases, about its severity. Conclusions. The oral cavity may be considered as a valuable clinical and biological interface in kidney disease. Careful oral examination, together with salivary and periodontal evaluation, may contribute to earlier recognition of systemic deterioration and support a more integrated, interdisciplinary approach to patients with CKD.

Keywords: chronic kidney disease, oral manifestations, saliva, periodontal disease, biomarkers, hemodialysis, oral-systemic health.

Introduction

Chronic kidney disease (CKD) is a progressive condition that has a strong impact on patients' quality of life and is associated with high morbidity and increased mortality. Besides its direct renal consequences, CKD is now widely recognized as a systemic disorder that can affect multiple organs, tissues and biological pathways [1, 2]. Because of this broader perspective, increasing attention has been directed toward the extra-renal manifestations of kidney disease, especially those involving the oral cavity, which is easy to examine during routine clinical practice and may reflect systemic imbalance in a visible and clinically useful way [3].

From a dental perspective, the oral cavity is more than simply an anatomical region affected by local pathology. It acts as a dynamic biological environment influenced by immunity, nutrition, salivary function, microbiota, and vascular status [3]. For this reason, oral findings in medically compromised patients may offer useful clues about underlying systemic conditions, disease progression and general inflammatory burden [3, 4]. In patients with CKD, this concept is especially relevant because renal dysfunction is associated with metabolic imbalance, mineral disturbances [2], chronic low-grade inflammation, immune dysregulation [4], and oxidative stress, all of which can influence the oral ecosystem [5].

The literature included in the present review suggests that oral abnormalities in CKD are both common and clinically significant. Frequently reported findings include xerostomia, mucosal pallor, taste disturbances, burning mouth sensation [5, 6], as well as gingival inflammation, increased calculus accumulation, higher plaque retention, dental caries, and periodontal disease [3]. These changes are often more evident in patients with advanced renal disease or in those receiving hemodialysis [5], but they are not limited to this stage. Importantly, oral and salivary abnormalities have also been documented in pre-dialysis patients, suggesting that the oral

cavity may begin to reflect renal impairment early in the course of this disease [5].

Among the various oral findings associated with CKD, saliva has become one of the most interesting elements [6]. One major practical advantage of saliva is that it can be collected non-invasively, repeatedly and with minimal discomfort, which makes it useful in both research and clinical settings [6]. Clinical studies have shown that CKD can be associated with reduced salivary flow [6] and altered salivary composition, including changes in relevant biochemical components [7]. More recently, research on salivary biomarkers has moved beyond descriptive findings. Proteomic work identified candidate proteins that may help distinguish CKD patients from healthy controls [8], while recent cross-sectional studies suggested that salivary creatinine and urea may also have diagnostic value as simple and non-invasive markers [3, 8].

Another major component of the oral-kidney relationship is periodontal disease. Current evidence points toward a bidirectional association between CKD and periodontitis [2]. On one hand, CKD may worsen periodontal status through chronic inflammation, impaired tissue repair, immune dysregulation, oxidative stress, and metabolic disturbances [2,4]. On the other hand, periodontal inflammation may contribute to the systemic inflammatory load through bacterial products, cytokine release [5,7], and chronic immune activation [6]. Because of this chronic immune activation, periodontal disease should not be interpreted only as an oral complication, but also as a condition that may reflect and possibly influence the systemic disease activity [6].

Recently, the discussion has extended beyond classic oral manifestations and now includes oral microbiological findings, tongue-related features and salivary proteomics [9]. Some studies have explored whether changes in the tongue surface [9] or saliva-related tongue characteristics [10] could provide additional information about CKD severity and dialysis status. Others have examined salivary biomarkers in an effort to move toward non-invasive diagnostic support [11, 12]. Although these approaches remain exploratory, they strengthen the broader idea that the oral cavity may serve not only as a site of complications, but also as a practical diagnostic interface in kidney disease [12, 13].

The topic is also highly relevant from the perspective of dental education and everyday practice. For a future dentist, recognizing oral changes associated with systemic disease is an essential part of comprehensive patient care [4]. In CKD, this means being able to identify suspicious mucosal changes, salivary dysfunction, gingival inflammation, or progressive periodontal destruction [14]. It is also important to understand that these findings may be linked to a broader medical condition [14, 7]. In this sense, the dentist may contribute not only to local treatment, but also to early referral, interdisciplinary communication, and better long-term care [7].

Therefore, the aim of the present systematic review was to evaluate the available evidence regarding oral clinical markers and pathophysiological correlates in CKD, with particular emphasis on oral manifestations [8], salivary changes [8,9], periodontal involvement [10, 12], microbiological findings [15], and their possible diagnostic significance.

Material and methods

This paper was designed as a systematic review with narrative synthesis and aimed to evaluate the main oral clinical markers reported in patients with chronic kidney disease, together with the biological mechanisms that may explain the link between oral findings and renal dysfunction.

The literature search was performed across PubMed/MEDLINE and Scopus, followed by manual screening of the reference lists of the selected papers. The search included articles published in English up to April 2026. The following search terms were used in different combinations: “chronic kidney disease”, “oral manifestations”, “oral cavity”, “saliva”, “salivary biomarkers”, “periodontal disease”,

"periodontitis", "xerostomia", "oral microbiota", "tongue", and "hemodialysis".

The inclusion criteria were: (1) original human studies and relevant review articles; (2) studies published in English; (3) full-text availability; (4) studies including patients with chronic kidney disease, pre-dialysis CKD, hemodialysis or end-stage kidney disease and (5) studies reporting oral clinical manifestations, salivary changes, periodontal parameters, microbiological observations, tongue-related features, or salivary biomarkers.

The exclusion criteria were: studies not focused on kidney disease, animal and in vitro studies, duplicate publications, papers without relevant oral clinical or biological data, and articles with limited relevance to the objective of this review.

After the initial search, all records were screened first by title and abstract. Potentially relevant papers were subsequently evaluated in full text.

In total, 54 records were identified through database and manual searches. After removing 11 duplicates, 43 records remained for screening. Following title and abstract evaluation, 19 papers were excluded. After this, 9 studies were excluded because they did not provide enough relevant data. Finally, 15 studies were included in the review. The study selection process is summarized in Figure 1.

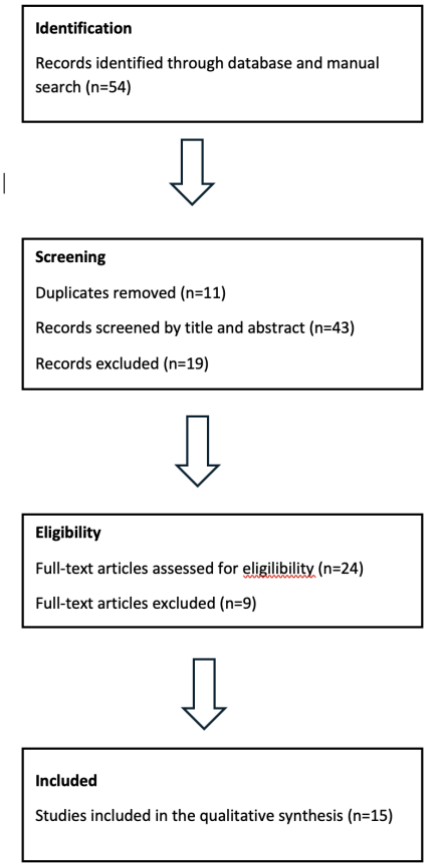

Figure 1. Flow Chart Of The Study Selection Process.

For each selected study, the following data were extracted: first author, year of publication, study design, study population characteristics, renal status or CKD stage, main oral variables assessed, principal findings and clinical relevance for the oral-kidney relationship. Because the included studies were considerably different in design, population, and outcomes, no meta-analysis was performed. Instead, we chose to analyze them using a narrative

synthesis approach and organized the findings into thematic categories: clinical oral manifestations, salivary changes and biomarkers, periodontal and microbiological findings, tongue-related indicators, and pathophysiological correlates.

The final synthesis was written with the intention to highlight both the practical and the clinical implications and the pathophysiological meaning of oral findings in kidney disease. The review was designed not only to summarize the literature but also to maintain a clear clinical perspective, providing highly relevant insights for interdisciplinary patient management and scientific practice.

Table 1. Inclusion and exclusion criteria used in the study selection

Inclusion criteria	Exclusion criteria
Original human studies and relevant review articles	Studies not focused on chronic kidney disease
Articles published in English	Animal studies
Full-text availability	In vitro studies
Studies including patients with CKD, pre-dialysis CKD, hemodialysis, or end-stage kidney disease	Duplicate publications
Studies reporting oral manifestations, salivary changes, periodontal findings, microbiological findings, tongue-related features, or salivary biomarkers	Articles without relevant oral clinical or biological data
Studies relevant to the objective of this review	Articles with limited relevance to the review aim

Results

A total of 15 studies with different methodological designs were included in the final synthesis. These studies covered a wide spectrum from observational and cross-sectional studies [3, 4, 10, 13] , to case-control studies [9,8], pilot studies [12,14], a randomized controlled clinical study [15] and review-based papers used to frame the broader clinical and biological significance of the oral-kidney relationship [2,4,6,10,12]. Taken together, these studies explored several interconnected aspects of the oral-renal relationship and helped map the available evidence from both clinical and biological perspectives [1,3,5,7,10,13].

The results of the present review are presented in Table 2.

Table 2. Main characteristics and findings of the included studies.

Ref.	Author, year	Study design	Study population/ focus	Main findings	Relevance to this review

[1]	Li et al.,2025	Review	Mechanistic links between periodontal disease and CKD	Proposed mechanisms included oral dysbiosis, systemic inflammation, oxidative stress, immune dysregulation, and renal fibrosis	Strong mechanistic support for the oral-kidney connection
[2]	Kumar et al.,2025	Hospital-based observational study	Patients with systemic disease and oral lesions	Periodontal disease, candidiasis, glossitis, aphthous ulcers and lichenoid reactions were commonly observed in medically compromised patients	Provides general support for the oral cavity as a site where systemic disease may become clinically visible
[3]	Costacurta et al.,2022	Review	CKD, nutritional status and oral disease	CKD was linked to malnutrition, vitamin imbalance, metabolic acidosis and low-grade inflammation, all potentially relevant to oral disease	Useful for the pathophysiological background linking systemic renal changes to oral health
[4]	Gheorghe et al.,2024	Cross-sectional study	Pre-dialysis CKD* patients; oral health, salivary function, biomarker profiles	Reduced salivary flow, poor dental status, gingival inflammation, and periodontal disease were common in pre-dialysis CKD Proposed mechanisms included oral dysbiosis, systemic inflammation, oxidative stress, immune dysregulation, and renal fibrosis	Supports the idea that oral and salivary changes may appear early, even before dialysis
[5]	Picolo et al., 2025	Pilot study	Salivary proteomics in CKD vs healthy controls	Identified candidate salivary biomarkers API5, PI-PLC and Sgsm2	Useful for future diagnostic perspectives and non-invasive biomarker discussion
[6]	Hoefer et al.,2024	Longitudinal randomized controlled study	Young CKD patients receiving intensive oral prophylaxis	Clinical gingival improvement was observed but not major change occurred in the tongue microbiome	Shows that preventive oral care is beneficial, even when microbial changes are limited

[7]	Baciu et al., 2023	Narrative review	CKD and periodontitis interplay	Emphasized systemic inflammation, oxidative stress, microbial imbalance and bidirectional oral-systemic interaction	Good conceptual support for the discussion section
[8]	Chen et al.,	Cross-sectional study	Tongue features associated with CKD	Certain tongue characteristics differed between CKD patients and controls	Adds supportive evidence for tongue-related diagnostic indicators
[9]	Dembowska et al.,2023	Case-control study	Hemodialysis patients vs. healthy controls; oral mucosa status	Higher prevalence of oral mucosal pathology in hemodialysis patients, especially xerostomia, taste disorder and burning mouth	Important clinical evidence for oral soft-tissue involvement in advanced CKD
[10]	Farooq et al.,2025	Comparative clinical study	CKD patients vs healthy controls; oral and salivary contents	CKD patients showed decreased salivary flow, mucosal pallor, calculus accumulation, gingival bleeding and salivary electrolyte alterations	Supports saliva and oral findings as possible indicators of renal dysfunction
[11]	Chung et al.,2023	Clinical study	Tongue diagnosis index in CKD	Tongue features such as ecchymosis, coating, and saliva-related changes were associated with CKD severity	Supports exploratory non-invasive diagnostic approaches based on oral findings
[12]	Li et al.,2021	Review	Periodontitis and CKD progression	Periodontitis may worsen CKD through oral flora, cytokines and oxidative stress	Reinforces the bidirectional inflammatory relationship between oral disease and renal disease
[13]	Misaki et al.,2026	Pilot study	CKD patients; oral Streptococcus mutans counts and proteinuria	Higher oral bacterial counts were associated with worse proteinuria; lower counts were linked to improvement over time	Suggests that oral microbial burden may have systemic relevance in CKD
[14]	Sankari et al.,2026	Cross-sectional study	Salivary creatinine and urea in CKD	Salivary creatinine and urea showed diagnostic potential as non-invasive biomarkers for CKD	Strengthens the salivary diagnostic component of the review

[15]	Martínez Nieto et al.,2024	Review	Periodontitis and CKD bidirectional relationship	Highlighted inflammation and oxidative stress as central shared pathways	Useful for strengthening the biologic plausibility of the oral-kidney axis

CKD - chronic kidney disease

Clinical oral manifestations in chronic kidney disease

The available evidence provides a clear overview: patients with CKD frequently present multiple oral abnormalities. The most frequent findings include xerostomia, mucosal pallor, burning sensations and altered taste [8, 10]. Clinicians also often observe gingival bleeding, heavy calculus accumulation and severe periodontitis [3, 10]. These changes may have a significant impact on patients' quality of life by affecting oral comfort, nutrition, and oral hygiene long before we begin to consider their deeper systemic implications [3].

The case-control study focusing on oral mucosa status reported significantly higher rates of mucosal lesions in hemodialysis patients compared with healthy individuals [10]. The most common findings included xerostomia, burning mouth sensation, and altered taste among the most frequent complaints [10]. These symptoms may easily be overlooked in a consultation focused only on teeth and periodontal tissues. Even so, oral manifestations are not restricted to end-stage disease [8].

The pre-dialysis studies included in the review showed that reduced salivary quantity, poor dental status, gingival inflammation and moderate to severe periodontal disease may already be present before dialysis begins [3]. This aspect is particularly important because it suggests that oral changes can appear relatively early in the disease development [3]. Also, more observational data support the broader idea that oral tissues can actively reflect systemic pathology [4], reinforcing the need for careful clinical examination [3, 10].

Salivary changes and salivary biomarkers

Salivary dysfunction was one of the most consistent findings across the included studies. Reduced salivary flow was associated with oral dryness, mucosal discomfort [3], plaque accumulation, and a less protective oral environment [3]. This is clinically relevant because saliva plays a major role in lubrication [3,10], antimicrobial defence, taste perception and maintenance of oral homeostasis [10].

Beyond salivary quantity, CKD also appeared to influence salivary composition. The included studies reported significant changes in salivary electrolytes [7], while newer research highlighted the diagnostic utility of salivary creatinine and urea as non-invasive markers correlated with renal dysfunction [13]. One of the strengths of the pre-dialysis data was that it linked salivary function with both oral clinical findings and renal status in the same patient group [3]. This is relevant because it shows that these salivary changes are not just laboratory observations but they are directly connected with clinical evidence such as gingival inflammation, poor oral status and periodontal involvement [3].

At a more exploratory level, pilot salivary proteomic studies identified candidate proteins, such as API5, PI-PLC and Sgsm2, that may help distinguish CKD patients from healthy controls [12]. In addition, more recent research on creatinine and urea suggested that these biomarkers may have practical diagnostic value in CKD [5]. Taken together, these findings support the idea that saliva has strong potential as a non-invasive diagnostic fluid [5].

Periodontal disease and oral microbiological findings

Periodontal disease was one of the most recurrent themes in the reviewed literature [2,3]. The evidence confirms that gingival inflammation and periodontal breakdown are

common in CKD and may be connected to systemic inflammation [3], oxidative stress [5], immune failure [2], and microbial dysbiosis [2,5]. This is clinically relevant because it places periodontal disease within the wider context of systemic disease rather than treating it as an isolated local problem [5].

The narrative and review papers included in the analysis helped explain why the association between CKD and periodontitis is increasingly taken seriously [1]. They described a bidirectional relationship in which CKD may create a hostile metabolic environment that essentially damages periodontal tissues [5,6]. On the other hand, periodontal inflammation may increase systemic inflammatory burden and potentially contribute to renal deterioration [5, 6].

The pilot study evaluating oral Streptococcus mutans count and proteinuria was particularly interesting from a clinical perspective [14]. While it did not prove a direct causal relationship, it suggested that higher oral bacterial counts may be associated with worse renal parameters [14]. These findings support a more integrated view of oral infections and systemic disease.

In contrast, the randomized trial involving young CKD patients showed that professional oral prophylaxis improved plaque levels and clinical gingival inflammation without major changes in the tongue microbiome [15]. This suggests that clinical improvement and microbiological changes do not necessarily happen at the same pace and at the same time [15].

Tongue-related findings and emerging diagnostic indicators

Several studies expanded the analysis beyond classic oral findings and explored whether tongue-related features could provide additional information about CKD [9,11]. These studies reported associations between tongue coating, ecchymosis, saliva-related tongue changes, and disease severity or dialysis status [11].

From a practical point of view, these findings should still be considered supplementary rather than central information. A dental clinician would not diagnose kidney disease based on the tongue's appearance alone [11,13]. However, such features may become more relevant in the future with the advancement of digital diagnostic tools and image-based analysis [11,13].

Pathophysiological correlates linking oral and renal disease

The included studies repeatedly pointed to several pathophysiological mechanisms that may explain the oral changes observed in CKD. Chronic inflammation appeared to be one of the most important factors [6]. CKD is associated with a persistent low-grade inflammatory state, while periodontitis may further increase this burden through local cytokine production and chronic immune activation [6].

Oxidative stress was another recurrent mechanism [5]. In both CKD and periodontitis, excessive oxidative activity may contribute to tissue damage and help explain the bidirectional connection between oral and renal pathology [5, 6].

Nutritional and metabolic changes were also relevant. CKD is often associated with malnutrition, metabolic acidosis, and disturbances in mineral balance [1], all of which may influence oral tissues and periodontal health [3,7]. Taken together, these mechanisms suggest that the oral cavity is shaped not only by local factors such as plaque and oral hygiene, but also by deeper systemic changes [1, 7].

Finally, dysbiosis and microbial involvement are relevant not only for the oral cavity alone but also within the larger oral-systemic structure [2]. Oral microbes do not work alone, they actively interact with these altered inflammatory and metabolic pathways [5], proving that the oral cavity may be viewed as both a target and a participant in these systemic disease processes [2, 5].

Discussion

Our findings in the present systematic review strongly support the idea that the oral cavity may offer useful clinical information in patients with chronic kidney disease. The oral changes described in the literature were not just isolated findings but part of a wider pattern that included manifestations ranging from xerostomia [1, 9, 13] and pale mucosa [3, 7] to severe gingival inflammation [10,6] and bacterial involvement [5, 11]. They appear too frequent and consistent to be considered incidental findings; rather, they seem to be part of a much larger systemic dysfunction [11].

One of the most important observations in this review is that oral changes appear at different stages of kidney disease [3]. We often tend to associate severe oral pathology exclusively with patients with end-stage renal failure or only in those on hemodialysis [7]. However, the evidence clearly shows that significant alterations such as salivary, gingival, periodontal, and mucosal changes start during the pre-dialysis stage [1, 3, 7]. This is clinically relevant because it suggests that oral examination may have value earlier in the course of the disease and not only in advanced stages [1, 3, 7].

From a practical point of view, xerostomia deserves significantly more attention. Dry mouth is a symptom frequently reported by patients and is easy to recognize in clinical practice, but its significance may sometimes be underestimated [7]. For patients with CKD, reduced salivary flow significantly impairs eating, swallowing, and taste perception [7], while simultaneously affecting plaque control and mucosal protection [1, 9]. Because of this, dry mouth should be considered not only a symptom, but also a clinically useful sign that may indicate a broader systemic problem [1,9].

The salivary findings are particularly valuable because they connect the symptoms with measurable biological changes [1]. Reduced salivary flow affects the local oral environment, while altered salivary composition may reflect renal dysfunction more directly [1,9]. This is one reason why saliva has become an important topic in this field [9]. It is easy to collect, non-invasive, and potentially useful for both local and systemic evaluation [1,9,13]. The study on salivary creatinine and urea adds practical relevance by suggesting that saliva could support non-invasive biochemical assessment in CKD [13], while salivary proteomic studies point toward future biomarker-based diagnostics [8].

Periodontal disease also deserves central attention in this discussion of oral health in CKD. The literature reviewed here supports a bidirectional and biologically plausible relationship between CKD and periodontitis [4, 10, 12]. CKD may worsen periodontal tissues through chronic inflammation, oxidative stress, nutritional imbalance, altered bone metabolism, and impaired host defence [2, 4, 10]. At the same time, periodontitis may maintain systemic inflammation through bacterial products, circulating mediators, and chronic immune stimulation [10, 12]. This is important because it places periodontal disease within a broader systemic context rather than considering it exclusively a local condition [10].

The microbial findings further support this concept. The pilot study relating oral Streptococcus mutans in correlation with proteinuria suggested that oral microbial burden may have more implications than previously assumed [11]. In the same direction, the randomized study in young patients with CKD showed that intensive oral prophylaxis improved plaque levels and gingival inflammation, even though major microbiome changes were not seen [5]. This is clinically important because it suggests that preventive oral control could matter not only for local periodontal stability but also for systemic inflammatory load [5, 11].

Studies that looked at tongue-related findings should be interpreted more carefully [14, 15]. Even so, they support the idea that visible changes in the oral soft tissues may sometimes reflect more than local pathology alone [14, 15]. As non-invasive diagnostic methods continue to improve, these findings may become more useful in the future [14, 15].

Another important point of the present review is the pathophysiological aspect of the findings. Many of them refer to similar biological mechanisms. Chronic inflammation, oxidative stress [10], immune failure [4], poor nutrition [2], and salivary alteration [1,9] appear repeatedly in the literature. This makes the oral-kidney relationship more convincing, because it suggests that these oral findings are not random but a part of a wider biological process [2, 4, 10].

For dental practice, the indications are quite clear. These findings suggest that in patients with CKD, oral examination should be thorough and should always be interpreted in relation to the patient's general condition [7]. Findings such as xerostomia, mucosal pallor, bleeding, and heavy calculus deposits should be seen as signs with a much wider clinical significance [7, 9]. For this reason, regular follow-up, preventive care and good communication with the medical team are fully justified [3, 7].

At the same time, the limitations of the current literature should also be considered. Several included studies have small sample sizes, pilot designs, cross-sectional designs or exploratory methods [5,11,13]. For this reason, some conclusions remain suggestive rather than definitive. The existing literature is strong enough to support clinical relevance but not strong enough to answer every biological question [11,13].

The oral cavity cannot replace standard nephrological investigations, but it can provide valuable clinical information about the patient's systemic health [4,9,10].

Future perspectives

More research is still needed in this area, especially studies with larger patient groups and a more uniform methodology, because the available data are still quite varied [1,5,7,8]. It would also be useful to have more longitudinal studies, because these could show more clearly whether oral changes progress together with kidney disease or improve when the systemic condition is better controlled [1,9,5]. Salivary biomarkers seem especially promising, mainly because saliva can be collected easily and non-invasively [8]. Markers such as salivary creatinine, urea, and some proteomic profiles may have future diagnostic applicability if their diagnostic value is confirmed in larger studies [8,13]. At the same time, newer approaches such as oral microbiome analysis or tongue-based digital evaluation may also become relevant, although they still require further clinical validation [5,14,15]. Another important step would be better collaboration between dentists and nephrologists [4,6,10], so that oral findings can be used more effectively in monitoring CKD patients [4,6,10].

Conclusions

The studies included in this review suggest that the oral cavity may represent an important diagnostic interface in chronic kidney disease. Oral findings such as xerostomia, mucosal changes, periodontal inflammation, and salivary alterations appear frequently in patients with CKD and may reflect broader systemic dysfunction.

The evidence reviewed in this paper suggests that oral examination has value not only for local diagnosis and treatment, but also for the recognition of clinically relevant systemic changes. Salivary assessment and periodontal evaluation seem to be especially important in this context.

Although some newer approaches, such as salivary biomarkers and tongue-based indicators, still need further validation, they show promising potential for future non-invasive diagnostics.

Overall, careful oral examination may support earlier recognition, better follow-up, and a more integrated interdisciplinary approach in patients with chronic kidney disease.

Author Contributions (CRediT Taxonomy)

Conceptualization, Formal analysis, Investigation, Resources, Visualization, Writing - original draft, Writing - review & editing: M.D.L.

Data curation, Methodology, Supervision, Validation, Project administration: M.A.M.

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During the preparation of this work the author(s) used Gemini Pro in order to verify grammatical accuracy and find suitable synonyms specific to the medical field. After using Gemini Pro, the author(s) reviewed and edited the content as needed and are fully responsible for the originality and integrity of the content of the manuscript.

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