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PREVALENCE OF RED, ORANGE, AND GREEN MICROBIAL COMPLEXES IN PERIODONTAL POCKETS OF CHRONIC KIDNEY DISEASE PATIENTS ON HEMODIALYSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

To verify the prevalence of specific microorganisms of red, green, and orange microbiological complexes in periodontal pockets of chronic kidney disease (CKD) patients on hemodialysis. This systematic review was conducted according to the PRISMA statement. The search strategy included two independent reviewers who searched the PubMed, Web of Science, Scopus, Cochrane, and Lilacs databases in August 2024, using MeSH terms and keywords defined with the PICOS acronym. The studies included were cross-sectional and published from 2007-2017 in English. The risk of bias and quality of evidence were assessed with the NIH Quality Assessment Tool for Observational Cohort and Cross-sectional Studies. Quantitative analysis with proportion meta-analysis was also performed. 4,737 studies were initially selected, and five were included. The study verified the prevalence of the green complex - *Aggregatibacter actinomycetemcomitans* (6.69%); the orange complex - *Prevotella intermedia* (16.85%) and *Prevotella nigrescens* (37.51%); and the red complex - *Treponema denticola* (29.11%), *Porphyromonas gingivalis* (49.45%), and *Tannerella forsythia* (56.37%), the most predominant microorganism. In the subgingival microbiota of CKD patients on hemodialysis, the red complex showed higher rates and prevalences, and *Tannerella forsythia* was the most common pathogen.

Keywords: Chronic kidney disease. Hemodialysis. Microbiology. Odontology. Periodontal disease.

1. Introduction

Chronic kidney disease (CKD) is a structural change in the kidney (glomerular, tubular, and endocrine) that is usually progressive and irreversible and reduces or limits the filtering capacity of kidneys, causing uremia and substance accumulation in the blood that must be filtered and expelled by the kidneys (Queiroz et al. 2013; Kitamura et al. 2019; Tavares et al. 2022). After establishing this medical diagnosis, one of the treatment options is dialysis and hemodialysis, the latter promoting blood filtration and removing metabolic degradation products and excess fluid (Lopes et al. 2014).

Periodontal disease (PD) refers to common inflammatory diseases known as gingivitis and periodontitis, which are caused by a pathogenic microbiota in the subgingival biofilm. Its progress causes infection and inflammatory disease of dental supporting tissues, which may cause tooth loss and allow the

formation of a periodontal pocket (Li et al. 2021; Dallepiane et al. 2023; Łasica et al. 2024). The onset of periodontitis is marked by a drastic change in the microbial flora of the region. *Streptococcus* and *Actinomyces* microorganisms, which prevail in a healthy periodontium, are gradually replaced with *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*. Eradicating the pathological microbiota may stop periodontal attachment loss (Londhe et al. 2018).

There is a bidirectional relationship between PD and CKD (Fisher et al. 2010). The presence of an infectious and chronic inflammatory process such as PD can negatively affect the progression of CKD (Bastos et al. 2011). The local inflammation in PD can potentially increase the severity of systemic diseases (Ozmeric et al. 2018). Periodontal pathogens can enter the bloodstream and cause silent systemic inflammation (Hajishengallis, 2015).

Despite speculations that CKD is closely associated with PD progression, detailed pathological features at the molecular level and the clinical significance of PD in CKD patients are not fully understood (Kitamura et al. 2019). Some time ago, bacterial species were identified in complexes in the subgingival plaque of gingival sulcus or periodontal pockets. These microbial complexes of the subgingival biofilm are classified into five groups: red, green, orange, yellow, and purple. Red and orange are the complexes most studied and related to the association of PD (Socransky et al. 1998).

Considering the high prevalence of PD in the world population, compromised periodontal health strongly impacts systemic diseases (Celeste et al. 2019). Periodontal pathogens can play a significant role in renal inflammation and the induction of renal dysfunction (Chopra and Sivaraman, 2019), but few studies exist on the oral microbiota in CKD patients (Castillo et al. 2007).

Thus, the present systematic review aims to present the prevalence of the microbiota of red, green, and orange complexes in the periodontal pockets of CKD patients on hemodialysis.

2. Material and Methods

Protocol and registration

This systematic literature review was registered in the Prospective International Register of Systematic Reviews (PROSPERO) under identification number CRD42020161794 and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (PAGE et al. 2021) statement recommendations.

Selection criteria

The selection criteria used the PICOS acronym: Participants – human permanent teeth with PD and CKD patients; Intervention or Exposure – microbiological assays in periodontal pockets; Comparison or Control – human permanent teeth without PD and patients without CKD; Primary outcomes – association of specific microbial complexes in periodontal pockets with CKD patients on hemodialysis; Studies included – clinical studies with collections in human patients.

Focused question

This systematic review addressed the following question: Is there a prevalence of the microbiota of red, green, and orange complexes in the periodontal pockets of chronic renal patients on hemodialysis compared to patients not on hemodialysis?

Inclusion criteria

The inclusion criteria used in this search stage were:

I. Studies investigating the microbiological profile in periodontal pockets of CKD patients with periodontitis in permanent teeth.

II. No date or language restrictions.

Exclusion criteria

The exclusion criteria used in this search stage were:

I. Studies in deciduous teeth.

II. Periodontal studies that do not describe the bacteria of red, orange, and green complexes.

III. Reviews, case reports, protocols, brief communications, personal opinions, letters, posters, conference abstracts, and laboratory research.

IV. Studies that do not associate microorganisms with CKD and hemodialysis.

V. Studies published in the Latin (Roman) alphabet.

VI. Full texts not found.

VII. Inadequate statistical analysis for the proposed study.

Search strategy

On August 30, 2024, two independent reviewers (D.J.G. and J.O.M.) searched the PubMed, Web of Science, Scopus, Cochrane, and Lilacs databases using MeSH terms and other keywords adapted to each database. The references were managed with reference software (EndNote X7; Thomson Reuters, Philadelphia, PA) and duplicate removal. Next, the references were exported to a specific systematic review application (Rayyan QCRI) (Ouzzani et al. 2016). A third reviewer (J.P.C.) managed the references and exported them to the application to advance the selection of studies and allow a double-blind selection at this first moment by the two reviewers (D.J.G. and J.O.M.).

Selection of studies

The studies were selected in two stages. The first stage used the Rayyan QCRI application (https://rayyan.qcri.org/users/sign_in), resulting in the initial search of 6.546 articles, of which 1,806 were duplicates. Also, the reviewers (D.J.G. and J.O.M.) independently read and blinded the titles and abstracts of 4,737 studies. A third reviewer demonstrated the results after the two reviewers individually selected the eligible articles. Of the included studies, there were 11 in common, and 20 showed conflict. The review coordinator (M.S.T.) resolved the conflicts and selected six articles due to their titles and abstracts. In the second stage, the same reviewers (D.J.C. and J.O.M.) independently read the six articles in full and applied the eligibility and exclusion criteria. A third reviewer (D.D.O.M.) resolved doubts and disagreements to obtain consensus. In both phases, three experts (C.M.; F.G.D. and T.M.D.) cross-checked every piece of information. The research team and the research coordinator (M.S.T.) resolved disagreements regarding the eligibility of the studies.

Data extraction

The two reviewers (D.J.G. and J.O.M.) independently extracted the data from each selected article. The variables extracted from each study included author, year of publication, country, participant characteristics (n, age), and outcome. The results were tabulated to store the information found and selected.

Data collection and data items

Two reviewers (D.J.G. and J.O.M.) independently collected the data. Relevant data for each study included study characteristics (authors, year of publication, and country), participants (sample size, age, and sex), outcomes, and conclusions. Information was also collected on periodontal characteristics such as probing depth, periodontal pocket location, tooth mobility, bone loss, the loss of clinical attachment level, and gingival bleeding.

Assessment of the risk of bias in individual studies and quality of evidence

The extracted data were evaluated with the items of the NIH Quality Assessment Tool for Observational Cohort and Cross-sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) (Ouzzani et al. 2016).

The 14 structured questions of the tool were adapted according to the quality of evidence of the included articles. Each reviewer (D.J.G. and J.O.M.) independently extracted the data, and a third reviewer (D.D.O.M.) resolved disagreements. Scores were assigned for methodological quality according to predetermined criteria, and a calculation was performed at the end. Thus, the articles within each criterion obtained a score evaluated as high (9-7), moderate (6-4), or low (3-0). The risk of bias was categorized as high when the study reached up to 49% of the "yes" score, moderate if it reached 50% to 69% of the "yes" score, and low when it reached 70% of the "yes" score.

Statistical analysis

A quantitative analysis was performed with a proportion meta-analysis to analyze the success rate using the MedCalc Statistical Software, version 14.8.1 (MedCalc Software, Ostend, Belgium). A meta-analysis was performed with the Review Manager (RevMan version 5.3. Copenhagen: The Cochrane Collaboration 2014) to determine the odds ratio. Heterogeneity was calculated with I^2, following the appropriate Cochrane Guidelines, and a value higher than 50% indicated substantial heterogeneity between studies (Cochrane Handbook for Systematic Reviews of Interventions, n.d.). Thus, random effects were applied to each analysis. The significance level was 5%.

3. Results

The initial electronic search resulted in 6,543 articles with the keywords used (Figure 1), retrieving 2,631 titles from the PubMed database, 2,782 from Scopus, 912 from Web of Science, 142 from Lilacs, and 76 titles from the Cochrane library. After the independent elimination of duplicates (n = 1,806), the titles and abstracts of 4,737 articles were read, and 4,731 were excluded for not addressing the subject and the green and orange bacterial complexes. Thus, seven studies were considered for inclusion and a full-text reading. One of these studies was excluded, and five were included in this review. Figure 1 shows the search strategy flowchart.

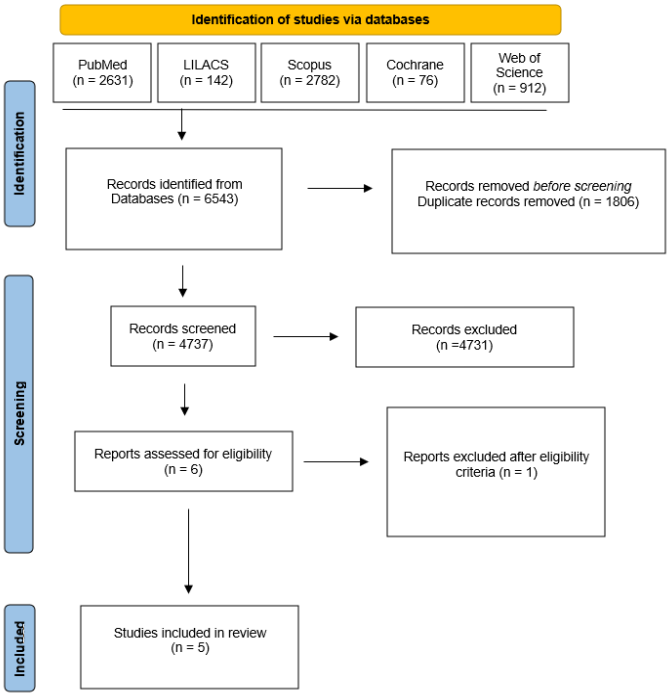

Figure 1. Search strategy flowchart.

Excluded studies

After reading the full texts of the six selected articles and applying the eligibility criteria, one study was excluded because it used patients on pre-dialysis and did not investigate the bacteria of green and orange complexes. Thus, five of the six articles initially selected were used in this systematic review. Table 1 presents the reasons for exclusions.

Table 1. Reasons for the exclusion and inclusion of articles.

Reference	First author (Year)	Reason for exclusion
1.	(Castillo et al. 2007)	Included
2.	(Takeuchi et al. 2007)	Included
3.	(Bastos et al. 2011)	Included
4.	(Ismail et al. 2015)	Excluded: CKD and pre-dialysis
5.	(Schmalz et al. 2016)	Included
6.	(Schmalz et al. 2017)	Included

Studies included

Five studies met the eligibility criteria of the present review. One was performed in Brazil, two in Germany, one in Spain, and one in Japan. All articles investigated the microbiota of periodontal pockets in CKD patients on hemodialysis. Overall, the five studies are cross-sectional and indicate the presence of microorganisms using similar measurement units, such as prevalence. The five studies used microbiological detection methods based on polymerase chain reaction (PCR).

Characteristics of the study participants

The selected studies included adult individuals between 29 and 79 years old with CKD, on hemodialysis, and with teeth diagnosed with PD. Patients were excluded from the study if they met at least one of the following exclusion criteria: patients subjected to periodontal treatment over the last six months of the study, smoking history, antibiotic and anti-inflammatory use six months before the study, pregnant or breastfeeding women, patients <18 years, uncontrolled diabetics, HIV carriers, convulsion or nervous disorder and inability to undergo an oral examination, organ transplantation (except for kidney), immune suppression, addicts (drugs or alcohol), infectious diseases (hepatitis A, B, and C; tuberculosis), lack of motor skills, other general illnesses that require medication.

Characteristics of interventions

Periodontal examinations were performed to determine the diagnosis. Thus, all studies identified that diagnosed teeth contained periodontal pockets >3 mm and evidence of attachment loss and gingival bleeding. Table 2 describes the periodontal clinical characteristics of the studies included in the systematic review.

Table 2. Clinical characteristics of periodontal parameters of the studies included.

Periodontal parameters							
Reference	**Periodontal pocket**	**Periodontal pocket location**	**Mobility**	**Bone loss**	**Clinical attachment loss**	**Gingival bleeding**	**Classification**
(Castillo et al. 2007)	>3mm	+1 site	NR	NR	Yes	Yes	NR
(Takeuchi et al. 2007)	>4mm	1 site	NR	NR	Yes	NR	NR
(Bastos et al. 2011)	>5mm	6 sites	NR	Yes	Yes	Yes	PC
(Schmalz et al. 2016)	>3mm	+1 site	NR	NR	Yes	Yes	PA
(Schmalz et al. 2017)	>3mm	2 sites	NR	NR	Yes	Yes	PM and PS

NR: Not reported; PM: Moderate periodontitis; PS: Severe periodontitis; PC: Chronic periodontitis; PA: Aggressive periodontitis.

Table 3 summarizes the risk of bias in the studies included in this systematic review according to the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. All five articles explained a research question (Item 1) and the characteristics of the study population (Item 2), recruited more than 50% of eligible participants (Item 3), detailed the eligibility criteria (Item 4), sample size (Item 5), exposure assessment at baseline (Item 6), and outcome measures (Item 11), and performed statistical analysis (Item 14). It was impossible to consider the deadline for the effect verification (Item 7) of different exposure levels (Item 8), exposure and evaluation measures (Items 9 and 10), blinding of outcome evaluators (Item 12), and follow-up rate (item 13) from the NIH Quality Assessment Tool.

Table 3: Quality assessment of the studies included according to the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

	References					
Question	Castillo *et al.* (2007)	Takeuchi *et al.* (2007)	Bastos *et al.* (2011)	Schmalz *et al.* (2016)	Schmalz *et al.* (2017)	**Total**
1. Research question	Yes	Yes	Yes	Yes	Yes	5
2. Study population	Yes	Yes	Yes	Yes	Yes	5
3. Participation rate of eligible persons	Yes	Yes	Yes	Yes	Yes	5
4. Eligibility criteria	Yes	Yes	Yes	Yes	Yes	5
5. Sample size	Yes	Yes	Yes	Yes	Yes	5
6. Exposure assessment	Yes	Yes	Yes	Yes	Yes	5
7. Deadline	NA	NA	NA	NA	NA	0
8. Exposure levels	NA	NA	NA	NA	NA	0
9. Exposure measures	CD	CD	CD	CD	CD	0
10. Repeated exposure assessment	NA	NA	NA	NA	NA	0
11. Outcome measures	Yes	Yes	Yes	Yes	Yes	5
12. Blinding of evaluators	NA	NA	NA	NA	NA	0
13. Follow-up rate	NA	NA	NA	NA	NA	0
14. Statistical analysis	Yes	Yes	Yes	Yes	Yes	5
TOTAL	8	8	8	8	8	

NA: Not applicable, CD: Cannot determine

The included articles did not verify all NIH Quality Assessment Tool items. The five articles met eight criteria, meaning that at least 50% were evaluated. Therefore, the risk of bias among the studies was moderate. Hence, the certainty of conclusions and strength of evidence were assessed by calculating the number of studies highlighting the presence of a specific microorganism.

Characteristics of outcome measures

All articles reported the microbial plaque composition of periodontal pockets. Table 4 shows a quantitative analysis of the tracked species.

4. Discussion

This study aimed to evaluate the pathogenic periodontal microbiota in individuals on hemodialysis to verify the interrelationship of studies and present the prevalence of periodontal bacteria of red, green, and orange complexes. In all studies, only chronic kidney disease (CKD) patients on hemodialysis were included in the meta-analysis. Studies have reported that the influence of the oral microbiota can extend beyond the oral cavity, affecting systemic conditions (Castillo et al. 2007; Rajasekaran et al. 2024). PD may become a source of infection, as CKD patients are susceptible to it due to the immunodeficiency caused by uremia (Queiroz et al. 2013).

Table 4. Prevalence studies of the bacteria of green, orange, and red complexes in periodontal pocket samples.

Meta-analysis (the number of studies included)	Cases	Total	Prevalence (95%CI)	I^2 (95% CI)	Forecast range
Red Complex					
Porphyromonas gingivalis (n=6)	141	303	49.45% (21.15-78.1%)	90% (81-95%)	(0.98-98.98%)
Tannerella forsythia (n=6)	161	303	56.37% (34.9-76.61%)	88% (76-94%)	(5.35-96.73%)
Treponema denticola (n=5)	72	251	29.11% (12.35-54.47%)	81% (55-92%)	(0.74-95.75%)
Orange Complex					
Prevotella intermedia (n=5)	47	303	16.85% (10.17-26.61)	69% (27-87%)	(3.46-53.38%)
Prevotella nigrescens (n=3)	58	115	37.51% (1.92-94.84)	89% (71-96%)	(0.00-100.00%)
Green Complex					
*Aggregatibacter actinomycetemcomitans (*n=5)	25	303	6.69% (2.07-19.56)	84% (68-92%)	(0.98-98.98%)

Our systematic literature review selected (Lopes et al. 2014) articles according to inclusion and exclusion criteria (Castillo et al. 2007; Takeuchi et al. 2007; Bastos et al. 2011; Schmalz et al. 2017). In complex microbial communities, quantification is crucial to understanding and modeling natural and designed ecosystems. Microbiological culture methods indicate limitations such as higher demand for culture media, the difficulty or impossibility of cultivating some species, control of microbial reproduction, adequate transport of samples, and laboratory conditions (Socransky et al. 2004; Bonk et al. 2018).

It has not been determined whether periodontal treatment and therapy can influence the regression of CKD (Takeuchi et al. 2007), but periodontal treatment reduces systemic inflammation and improves the glomerular filtration rate, thus contributing to CKD improvement (Ismail et al. 2015; Delbove et al. 2021). Periodontal disease treatment requires the pathogenic role of bacteria accumulated in the periodontal pocket to be recognized. Chemical and mechanical therapy alone cannot eliminate all the bacteria involved in PD, but decreasing the bacterial quantity and controlling modifying factors can paralyze disease activity (Chopra and Sivaraman 2019).

Studies on the association between periodontal diseases and CKD (Li et al. 2021; Ferreira et al. 2024; Yang et al. 2024) have emerged and attempted to demonstrate a bidirectional relationship between the conditions. The mechanisms potentially involved in the bidirectional association are the capability of proinflammatory cytokines to induce endothelial dysfunction and atherogenesis (Chambrone et al. 2013) and molecular mimicry of bacterial heat shock proteins secreted in response to endothelial injury, which induce atheroma formation (Fischer et al. 2009). Given such systemic effects, periodontitis is a non-traditional risk factor for CKD. Permanent systemic inflammation in periodontal patients and the possibility of damage to the kidney endothelium by circulating periodontal bacteria might increase the risk of CKD (Chen and Li 2024).

In the present systematic review, the prevalence of bacteria of the red complex was *Treponema denticola* (29.11%), *Porphyromonas gingivalis* (49.45%), and *Tannerella forsythia* (56.37%); the orange complex was *Prevotella nigrescens* (37.51%) and *Prevotella intermedia* (16.85%); the green complex was *Aggregatibacter actinomycetemcomitans* (6.69%) in CKD and periodontal disease patients.

Tannerella forsythia is a Gram-negative anaerobic member of the *Cytophaga-Bacteroides* family (Tanner et al. 1986). It is one of the most prominent inhabitants of the subgingival biofilm crucial to causing periodontitis (Pham et al. 2010). *Tannarella forsythia* is an independent risk factor for periodontal disease in CKD patients. In a cohort study by Ismail et al. (2015), CKD was not significantly associated with a particular subgingival periodontal pathogen profile in periodontitis patients.

Castillo et al. (2019) concluded that the *Tannerella forsythia* pathogen was the most prevalent in individuals undergoing hemodialysis, interacting with other members of the oral plaque biofilm and evading host defenses (Sutherland 2001). These patients had a higher number of periodontal-pathogenic microorganisms than a control group. The authors did not observe a significant relationship between long-term hemodialysis and periodontal pockets, specific microbiota, or biofilm composition. Takeuchi et al. (2007) found a significantly higher detection rate for *Tannerella forsythia*, *Treponema denticola*, and *Prevotella nigrescens* in the disease group than in the control group.

Treponema denticola is an anaerobic periodontal pathogen - a spirochete - and it has been linked to PD and its progression along with other Gram-negative bacteria. The accumulation of these pathogens and their products in the periodontal pocket can make the cells lining the periodontium susceptible to lysis and damage. *Treponema denticola* adheres to fibroblasts and produces several deleterious factors that can contribute to the virulence of bacteria (Sela 2001).

However, Bastos et al. (2011) showed that *Porphyromonas gingivalis* was the most frequent pathogen in the hemodialysis group and found *Tannerella forsythia*, concluding that red-complex bacteria were more frequent in patients with periodontitis and CKD than in healthy individuals (Bastos et al. 2011). The same was found by Mahendra et al. (2022), who demonstrated that red complex bacteria are prevalent in periodontitis and CKD patients, developing a different pathogenic mechanism interlinking the risk of CKD and periodontitis. *Porphyromonas gingivalis* is a Gram-negative oral anaerobic bacterium that participates in the pathogenesis of periodontitis. This bacterium can become highly destructive and proliferate in numerous cells in periodontal lesions due to its array of specialized virulence factors (Mysak et al. 2014).

Species of the red complex are found in a higher proportion as they move from supragingival to subgingival and from health to disease (Socransky and Haffajee 2002). Species of the orange complex proceed to colonization by species of the red complex. The red complex has a strong relationship with pocket depth and bleeding on probing and showed a stronger relationship with the most significant clinical parameters in the periodontal diagnosis (Socransky et al. 1998).

Aggregatibacter actinomycetemcomitans is a Gram-negative *Capnophilic coccobacillus*, small, non-motile, saccharolytic, round-ended, and saccharolytic rod, and a periopathogenic bacterium associated with localized aggressive periodontitis. Although different serotypes of *Aggregatibacter actinomycetemcomitans* have differential virulence factor expressions, the presence of cytolethal distention toxin, leukotoxin, and lipopolysaccharide has been more extensively studied in the context of modulating host immune response and conserving the infection (Herbert et al. 2016). *Aggregatibacter actinomycetemcomitans* is a potential periodontal pathogen due to its higher detection frequency and the high number presented in periodontitis lesions (Socransky et al. 2004; Bonk et al. 2018)**.**

Prevotella intermedia and *Prevotella nigrescens* belong to the orange complex and are among the species most frequently found in the subgingival plaque closely associated with PD[12]. *Prevotella intermedia*, a Gram-negative anaerobe, is a periodontal pathogen in advanced periodontitis and acute necrotizing ulcerative gingivitis (Haffajee and Socransky 1994).

Prevotella nigrescens and *Prevotella intermedia* present highly dynamic genomes and can take on various exogenous factors through horizontal gene transfer. They may represent crucial substances in the subgingival plaque, which can change microbial and environmental dynamics in the subgingival microbial ecosystem. That provides insight into the potential of *Prevotella intermedia* and *Prevotella nigrescens* as targets for effective interventions in periodontal disease. Factors related to genome modification and recombination indicate that *Prevotella* isolates at disease sites may be more capable of genomic reconstruction. Such microbiological groups have more unique virulence factors related to capsule and lipopolysaccharide syntheses, secretion systems, proteinases, and toxins, suggesting that disease-site strains may show a more specific virulence, particularly *Prevotella intermedia* (Schmalz et al. 2016).

Furthermore, the prevalence of these specific bacteria from the subgingival microbiota may help understand the microbiological profiles of the patients involved and correlate them with possible existing clinical and systemic conditions. It may also help repair this pathology with therapeutic approaches for disease control. Tavares et al. (2022) stated that periodontal treatment therapy may help CKD patients' prognosis and improve their quality of life, which must be considered.

Finally, this study's methodological limitation is the low number of articles included because few studies have investigated these specific bacterial complexes and their relationship with CKD. Thus, further investigation of this subject is required.

5. Conclusions

Among the results and limitations of the present study, *Tannerella forsythia* was the most predominant pathogen in the red complex, with a prevalence of 56.37%, followed by *Porphyromonas gingivalis* with 49.45%, and *Treponema denticola* 29.11%. In the green and orange complexes, *Aggregatibacter actinomycetemcomitans* (6.69%), *Prevotella nigrescens* (37.51%), and *Prevotella intermedia* (16.85%) prevailed.

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Conflicts of Interest: The authors declare no conflicts of interest.

Ethics Approval: PROSPERO database [CRD42020161794].

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