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PREVALENCE OF ORAL INJURIES AND SALIVARY CHANGES IN PATIENTS WITH CHRONIC RENAL FAILURE ON HEMODIALYSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

The objective of this study was to evaluate whether individuals with chronic renal failure (CRF) undergoing hemodialysis treatment have more salivary and oral mucosa alterations when compared to healthy individuals, through a systematic review followed by meta-analysis. A systematic literature review was performed, evaluating randomized clinical trials found in the Proquest, Embase, Scopus, Cochrane Library, Web of Science, Lilacs and Pubmed databases, using MeSH terms and other keywords. Initially, 40 articles were included in the study and, after reading the complete articles, only 15 clinical trials that analyzed oral lesions and salivary changes in patients with CRF undergoing hemodialysis treatment were eligible. Most of the clinical studies included were cross-sectional and composed of a study group and a control group. The mean age of participants in the study group was 50.19 years and in the control group, 48.95 years. The most common oral alterations found in the CRF group in relation to the control group were xerostomia, uremic breath, dysgeusia, coated tongue, gingival bleeding, and pale mucosa. The salivary flow of patients with CRF was 46.6% lower than the control group. The salivary pH in the study group was also more alkaline when compared to the control group. Greater amounts of urea, phosphate, C-reactive protein and total proteins were found in the saliva of individuals with CRF. Individuals with CRF undergoing hemodialysis are more prone to changes in both the quantity and quality of saliva, as well as having a greater amount of oral changes.

Keywords: Chronic Renal Failure. Salivary pH. Hyposalivation. Salivary Changes. Xerostomia.

1. Introduction

Chronic renal failure (CRF) is a process that occurs slowly, gradually and progressively. The same happens when the kidney suffers a persistent problem for more than three months. In general, CRF is characterized as an abnormality of the structure of the kidneys and/or loss of their filtering functions, causing the definitive loss of their functions (Jones et al. 2015).

It is estimated that CRF has a worldwide prevalence of 11% to 13% among adults (Hill et al. 2016). In the United States, approximately 11% of the population has CRF at some stage of evolution (Third National Health and Nutrition Examination Survey). In mainland China, the prevalence of CRF is reported to be 10.8% (Liu 2013). In Brazil, the prevalence is approximately 9% (Barreto et al. 2016). Currently, between 30% and 50% of cases of end-stage CRF in industrialized countries are due to diabetes and hypertension (Kitamura et al. 2019).

As a result of weakened immunity, most patients with CRF carry other illnesses that contribute to the worsening of their systemic condition (Queiroz et al. 2013). Due to fluid restriction and side effects of drug therapy (constant use of diuretics), it is common for individuals with CRF to develop changes in the oral cavity such as xerostomia. The systematic review and meta-analysis by Rodrigues et al. (2022) found that patients with chronic kidney disease presented lower salivary flow rate, higher pH, and higher phosphorus concentration in saliva. Insufficient salivary flow results in three general effects: (1) reduced bolus preparation, (2) reduced taste, and (3) increased susceptibility of oral structures to the disease (Pham and Le 2019).

The normal pH of saliva is 6 to 7, which means it is slightly acidic. Normal flow for unstimulated saliva is slightly greater than 0.1 mL/min and salivary pH can range from 5.3 to 7.8 (Kumar et al. 2020).

Saliva is a valuable oral fluid and is essential for the preservation and maintenance of oral health. However, it receives little attention until the quantity or quality declines. In addition, saliva acts as an antibody to bacterial antigens and works to aggregate or group bacteria, thus inhibiting bacterial binding to host tissues. Salivary glands secrete fluid containing immunological and non-immunological agents to protect teeth and mucosal surfaces. The immunological content of saliva includes: IgA, IgG and IgM. The non-immune salivary contents are: proteins, mucins, peptides and enzymes (Kumar et al. 2020).

The reflex of systemic pathological conditions in the oral cavity is thoroughly researched due to the multidisciplinary approach that has recently been addressed (Yamashita et al. 2013). In addition, changes in the oral cavity have been associated with increased morbidity and mortality in patients with CRF, however, this factor is often neglected. Advanced age and common comorbidities, such as diabetes and concomitant medications with immune dysfunction states, may also increase the risk of consequences for periodontal disease and other oral pathologies in individuals with CRF (Akar et al. 2011).

Thus, it is extremely important that dentists know if patients with CRF undergoing hemodialysis treatment present salivary alterations and oral diseases on a larger scale than with healthy individuals. With greater knowledge about this population and their needs, it will be easier to prevent and treat possible injuries to the oral cavity and also improve the general health of these individuals, preventing them from being affected by opportunistic infections related to the immune system.

Thus, the present study aims to evaluate, which are the most common oral lesions and salivary alterations in individuals with CRF undergoing hemodialysis treatment, through a systematic literature review followed by meta-analysis. The hypothesis of this study is that, due to systemic health conditions, patients with CRF undergoing hemodialysis have a higher prevalence of oral lesions and changes in salivary quantity and quality.

2. Material and Methods

Protocol and registration

A systematic literature review was carried out, registered on the Prospective International Registry of Systematic Reviews (PROSPERO) platform with the identification number CRD42021237144, and conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Page et al. 2021).

Search strategy

The individual search strategy was elaborated through electronic databases: Proquest, Embase, Scopus, Cochrane Library, Web of Science, Lilacs and Pubmed. Searches were performed from November

2020 to December 2020 through two independent reviewers (V.C.S. and D.J.G.), using MeSH terms and other keywords (Table 1). The search was carried out in articles without distinction of year and language. For the search, a Kappa agreement test (index of 0.90) was performed by the researchers regarding the adequacy of the studies to select the inclusion and exclusion criteria.

The acronym PICOS was introduced to define the eligibility criteria: Population: adults with chronic renal failure undergoing hemodialysis treatment; Intervention: oral changes, flow measurement and salivary composition determination; Control: individuals without chronic renal failure; Result: oral lesions and qualitative or quantitative salivary changes in people with chronic renal failure undergoing hemodialysis; and Study Design: clinical trials, cross-sectional case-control studies and cohort studies. The focused question addressed was: "What is the prevalence of oral lesions and salivary alterations in patients with chronic renal failure undergoing hemodialysis?".

Table 1. Search strategy.

Proquest	Search: ALL("Xerostomia" OR "Xerostomias" OR "Hyposalivation" OR "Hyposalivations" OR "sjogren syndrome" OR "sicca syndrome" OR "salivary gland stones" OR "Mouth Dryness" OR "Dryness" OR "Mouth" OR "Disease" OR "mouth diseases" OR "Mouth" OR "Mouth Disease") AND ALL("Concentration" OR "Hydrogen Ion Concentrations" OR "Hydrogen Ion" OR "Hydrogen Ion Concentration" OR "Hydrogen Ion Concentrations" OR "pH") AND ALL("CDK" OR "hemodialyses" OR "HD" OR "chronic kidney disease" OR "chronic kidney failure" OR "renal insufficiencies" OR "chronic renal failure" OR "renal dialysis" OR "renal hemodialysis" OR "renal transplantation" OR "renal transplantations" OR "failure" OR "kidney failure" OR "renal failures" OR "kidney failures" OR "kidney" OR "kidney insufficiencies" OR "kidney insufficiency" OR "renal failure") AND ALL("Manifestation" OR "Oral Manifestations" OR "Oral Manifestation" OR "Oral" OR "buccal mucosa" OR "Mucosa" OR "mouth mucosa" OR "Oral" OR "oral mucosa")	116
Embase	Search: TS=('Xerostomia' OR 'Xerostomias' OR 'Hyposalivation' OR 'Hyposalivations' OR 'sjogren syndrome' OR 'sicca syndrome' OR 'salivary gland stones' OR 'Mouth Dryness' OR 'Dryness' OR 'Mouth' OR 'Disease' OR 'mouth diseases' OR 'Mouth' OR 'Mouth Disease') AND TS=('Concentration' OR 'Hydrogen Ion Concentrations' OR 'Hydrogen Ion' OR 'Hydrogen Ion Concentration' OR 'Hydrogen Ion Concentrations' OR 'pH') AND TS=('CDK' OR 'hemodialyses' OR 'HD' OR 'chronic kidney disease' OR 'chronic kidney failure' OR 'renal insufficiencies' OR 'chronic renal failure' OR 'renal dialysis' OR 'renal hemodialysis' OR 'renal transplantation' OR 'renal transplantations' OR 'failure' OR 'kidney failure' OR 'renal failures' OR 'kidney failures' OR 'kidney' OR 'kidney insufficiencies' OR 'kidney insufficiency' OR 'renal failure') AND TS=('Manifestation' OR 'Oral Manifestations' OR 'Oral Manifestation' OR 'Oral' OR 'buccal mucosa' OR 'Mucosa' OR 'mouth mucosa' OR 'Oral' OR 'oral mucosa')	1.520
Scopus	Search: TITLE-ABS-KEY("Xerostomia" OR "Xerostomias" OR "Hyposalivation" OR "Hyposalivations" OR "sjogren syndrome" OR "sicca syndrome" OR "salivary gland stones" OR "Mouth Dryness" OR "Dryness" OR "Mouth" OR "Disease" OR "mouth diseases" OR "Mouth" OR "Mouth Disease") AND TITLE-ABS-KEY("Concentration" OR "Hydrogen Ion Concentrations" OR "Hydrogen Ion" OR "Hydrogen Ion Concentration" OR "Hydrogen Ion Concentrations" OR "pH") AND TITLE-ABS-KEY("CDK" OR "hemodialyses" OR "HD" OR "chronic kidney disease" OR "chronic kidney failure" OR "renal insufficiencies" OR "chronic renal failure" OR "renal dialysis" OR "renal hemodialysis" OR "renal transplantation" OR "renal transplantations" OR "failure" OR "kidney failure" OR "renal failures" OR "kidney failures" OR "kidney" OR "kidney insufficiencies" OR "kidney insufficiency" OR "renal failure") AND TITLE-ABS-KEY("Manifestation" OR "Oral Manifestations" OR "Oral Manifestation" OR "Oral" OR "buccal mucosa" OR "Mucosa" OR "mouth mucosa" OR "Oral" OR "oral mucosa")	2.305
Cochrane library	Search: (Xerostomia" OR "Xerostomias" OR "Hyposalivation" OR "Hyposalivations" OR "sjogren syndrome" OR "sicca syndrome" OR "salivary gland stones" OR "Mouth Dryness" OR "Dryness" OR "Mouth" OR "Disease" OR "mouth diseases" OR "Mouth" OR "Mouth Disease")):ti,ab,kw AND ("Concentration" OR "Hydrogen Ion Concentrations" OR "Hydrogen Ion" OR "Hydrogen Ion Concentration" OR "Hydrogen Ion Concentrations" OR "pH")):ti,ab,kw AND ("CDK" OR "hemodialyses" OR "HD" OR "chronic kidney disease" OR "chronic kidney failure" OR "renal insufficiencies" OR "chronic renal failure" OR "renal dialysis" OR "renal hemodialysis" OR "renal transplantation" OR "renal transplantations" OR "failure" OR "kidney failure" OR "renal failures" OR "kidney failures" OR "kidney" OR "kidney insufficiencies" OR "kidney insufficiency" OR "renal failure")):ti,ab,kw AND ("Manifestation" OR "Oral Manifestations" OR "Oral Manifestation" OR "Oral" OR "buccal mucosa" OR "Mucosa" OR "mouth mucosa" OR "Oral" OR "oral mucosa"):ti,ab,kw	2.330

Table 1. Continued.

Web of Science	Search: TS=("Xerostomia" OR "Xerostomias" OR "Hyposalivation" OR "Hyposalivations" OR "sjogren syndrome" OR "sicca syndrome" OR "salivary gland stones" OR "Mouth Dryness" OR "Dryness" OR "Mouth" OR "Disease" OR "mouth diseases" OR "Mouth" OR "Mouth Disease") AND TS=("Concentration" OR "Hydrogen Ion Concentrations" OR "Hydrogen Ion" OR "Hydrogen Ion Concentration" OR "Hydrogen Ion Concentrations" OR "pH") AND TS=("CDK" OR "hemodialyses" OR "HD" OR "chronic kidney disease" OR "chronic kidney failure" OR "renal insufficiencies" OR "chronic renal failure" OR "renal dialysis" OR "renal hemodialysis" OR "renal transplantation" OR "renal transplantations" OR "failure" OR "kidney failure" OR "renal failures" OR "kidney failures" OR "kidney" OR "kidney insufficiencies" OR "kidney insufficiency" OR "renal failure") AND TS=("Manifestation" OR "Oral Manifestations" OR "Oral Manifestation" OR "Oral" OR "buccal mucosa" OR "Mucosa" OR "mouth mucosa" OR "Oral" OR "oral mucosa") AND DOCUMENT TYPES: (Article)	1.101
Lilacs	Search: Tw=("Xerostomia" OR "Xerostomias" OR "Hyposalivation" OR "Hyposalivations" OR "sjogren syndrome" OR "sicca syndrome" OR "salivary gland stones" OR "Mouth Dryness" OR "Dryness" OR "Mouth" OR "Disease" OR "mouth diseases" OR "Mouth" OR "Mouth Disease") AND tw=("Concentration" OR "Hydrogen Ion Concentrations" OR "Hydrogen Ion" OR "Hydrogen Ion Concentration" OR "Hydrogen Ion Concentrations" OR "pH") AND tw=("CDK" OR "hemodialyses" OR "HD" OR "chronic kidney disease" OR "chronic kidney failure" OR "renal insufficiencies" OR "chronic renal failure" OR "renal dialysis" OR "renal hemodialysis" OR "renal transplantation" OR "renal transplantations" OR "failure" OR "kidney failure" OR "renal failures" OR "kidney failures" OR "kidney" OR "kidney insufficiencies" OR "kidney insufficiency" OR "renal failure" AND tw=("Manifestation" OR "Oral Manifestations" OR "Oral Manifestation" OR "Oral" OR "buccal mucosa" OR "Mucosa" OR "mouth mucosa" OR "Oral" OR "oral mucosa")	1.225
Pubmed	Search: ("Xerostomia[Mesh Terms]" OR "Xerostomias[Mesh Terms]" OR "Hyposalivation[Mesh Terms]" OR "Hyposalivations[Mesh Terms]" OR "sjogren syndrome[MeSH Terms]" OR "sicca syndrome[MeSH Terms]" OR "Mouth Dryness[Mesh Terms]" OR "salivary gland stones[MeSH Terms]" OR "Dryness" OR "Mouth" OR "Disease" OR "mouth diseases[MeSH Terms]" OR "Mouth" OR "Mouth Disease[Mesh Terms]") AND ("Concentration" OR "Hydrogen Ion Concentrations[Mesh Terms]" OR "Hydrogen Ion[Mesh Terms]" OR "Hydrogen Ion Concentration[Mesh Terms]" OR "Hydrogen Ion Concentrations[Mesh Terms]" OR "pH") AND ("CDK" OR "hemodialyses[MeSH Terms]" OR "HD" OR "chronic kidney disease" OR "chronic kidney failure[MeSH Terms]" OR "renal insufficiencies[MeSH Terms]" OR "chronic renal failure[MeSH Terms]" OR "renal dialysis" OR "renal hemodialysis" OR "renal transplantation[MeSH Terms]" OR "renal transplantations[MeSH Terms]" OR "failure" OR "kidney failure[MeSH Terms]" OR "renal failures[MeSH Terms]" OR "kidney failures[MeSH Terms]" OR "kidney" OR "kidney insufficiencies[MeSH Terms]" OR "kidney insufficiency[MeSH Terms]" OR "renal failure[MeSH Terms]" AND ("Manifestation" OR "Oral Manifestations[Mesh Terms]" OR "Oral Manifestation[Mesh Terms]" OR "Oral" OR "buccal mucosa[MeSH Terms]" OR "Mucosa" OR "mouth mucosa[MeSH Terms]"OR "Oral OR "oral mucosa[MeSH Terms]")	1.813

Selection of studies

A study selection strategy was developed in two phases. In phase one, the titles and abstracts of the studies were examined by two independent researchers (V.C.S. and D.J.G.), verifying which ones were eligible. In phase two, the studies were completely read by the same independent reviewers to verify if they were within the inclusion and exclusion criteria. Any disagreements were resolved through discussion. In case of any disagreement or discrepancy, a third independent reviewer (K.A.S.C) was consulted to reach a consensus. In both phases, a team of four specialists (F.C.V., L.C.D., T.M.D. and M.S.T.) verified all the information. If any disagreement about eligibility remained, it was discussed between the research team and the coordinator (J.P.C.).

Data collect

Data extraction was performed by two independent researchers (V.C.S. and D.J.G.). The variables extracted from each selected article included: type of study, sample size, population, details of salivary

parameters, gender, mean age, presence of lesions and presence or absence of a control group. Data were attached to an Excel spreadsheet to store the information found/selected.

Statistical analysis

A quantitative analysis was performed using proportion meta-analysis in order to analyze the success rate using MedCalc Statistical software version 14.8.1 (MedCalc Software, Ostend, Belgium). To analyze the odds ratio, a meta-analysis was performed with Review Manager (RevMan version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

Heterogeneity was calculated by I^2, following the appropriate Cochrane Guidelines, with a value greater than 50% being considered an indicator of substantial heterogeneity between studies (Higgins and Green 2011). Thus, the random effect was applied to each analysis. As for the level of significance, it was set at 5%.

Risk of bias in individual studies

The risk of bias (RoB) of individual studies was assessed using the Joanna Briggs Institute Critical Assessment Checklist specific to quasi-experimental (non-randomized) (Waddington et al. 2017), cohort (Murphy 2021), and randomized controlled trials (Kennedy et al. 2019). The RoB evaluation of the included articles was performed independently by two reviewers (V.C.S. and D.J.G.), the information was cross-checked and a consensus was established in a meeting. In case of disagreement, a third reviewer was consulted to make the final decision (K.A.S.K.C). Following Joanna Briggs' guidelines, decisions about the scoring system and cut-off points were agreed upon by all reviewers prior to the assessment. Studies that reached up to 49% were scored “yes” and classified as “high RoB”; 50% to 69% as “Moderate RoB”; and more than 70% as “low RoB” (Souza et al. 2020).

Assessment of the quality of evidence

The extracted data were evaluated according to the items of the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NIH 2017). The questionnaire was adapted and structured with 14 questions regarding the quality of evidence of the selected articles. Thus, the reviewers independently extracted the collected data. Thus, scores for methodological quality were assigned according to predetermined criteria. Finally, a calculation was added to these distributed scores. For this, the articles within each criterion had a score evaluated as high (9-7), moderate (6-4) or low (3-0) for each study.

3. Results

Search results

The initial electronic search resulted in a total of 10,410 articles (1,813 articles from the Pubmed database, 1,225 titles from the SciELO and Lilacs databases, 1,520 articles from the Embase database, 2,330 articles from the Cochrane database, 2,305 titles from the database Scopus database, 1,101 titles from the Web of Science database and 116 articles from the Proquest database). After the independent elimination of 3,965 duplicate articles, 6,445 were left to be evaluated in phase 1, where the selection of studies was made by reading the title and abstract. Thus, 40 articles were considered for inclusion in phase one. During phase 2 of the selection, the eligibility criteria were applied, and 15 articles were selected to be included in the review after its complete reading. The search strategy flowchart is shown in Figure 1.

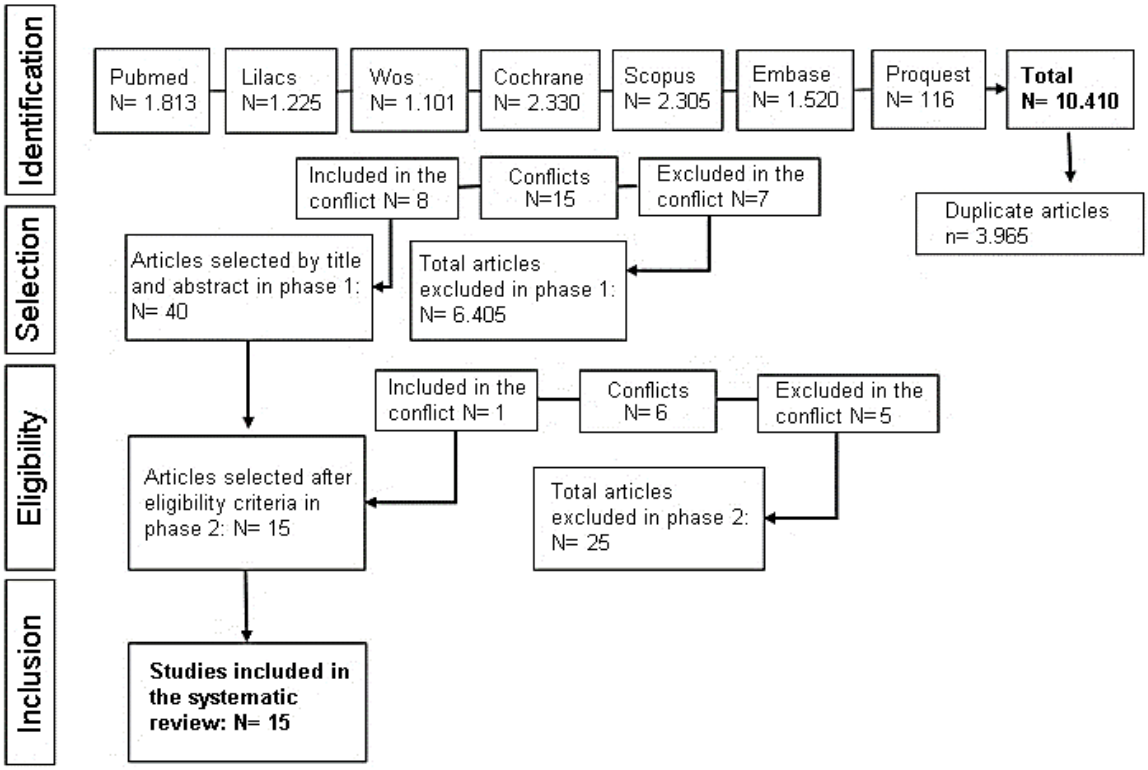

Figure 1. Search strategy flowchart.

After applying the selection criteria for title and abstract, 32 articles were included by both reviewers and 15 articles conflicted. Of these 15 articles in conflict, 8 were included and 7 were excluded because: they evaluated individuals under 18 years of age; articles without full text; individuals without CRF; transplanted individuals; duplicate studies; case report studies; microbiological studies only and literature reviews. After agreement, a total of 40 articles were selected for full reading and application of eligibility criteria.

Exclusion from Studies

After the complete reading of the 40 studies included in phase 1, 25 articles were excluded: 2 studies in which patients did not have CRF and were not on hemodialysis treatment; 11 studies that did not have a healthy control group; 4 studies where the minimum age was not respected; 1 study where the relationship between CRF and salivary alterations was not investigated; 6 studies that were not published in English or Portuguese; 1 study for not showing coherence or for having a dubious or difficult to understand methodology (Table 2).

Studies included

The study included 15 articles containing clinical research of patients diagnosed with CRF and treated with hemodialysis, along with a healthy control group. The oldest study was from the year 2007 and the most recent was from the year 2020. The average age of all participants in the study group was 50.19 years and in the control group it was 48.95 years. In both groups there were both males and females. The countries where the surveys were carried out are: India, Turkey, Northern Macedonia, China, USA, Iran, Serbia, Brazil and Vietnam. The studies evaluated salivary changes, such as: salivary flow, salivary pH, buffer capacity, urea, total proteins, ammonia, albumin, sodium, chloride, potassium, calcium, phosphate, tumor necrosis factor alpha, interleukin 6, creatinine, IgA, IgG, nitrous oxide, C-reactive protein. It was also verified in the study, subjects with the presence of oral alterations and lesions, such as: pale mucosa, xerostomia, gingival bleeding, dysgeusia, uremic breath, petechiae and ecchymosis, coated tongue, burning tongue, gingival enlargement, oral ulcer, red lesions, white spot keratosis, pigmented lesions, mucosal defects, white lesions,

potentially malignant lesions, and uremic stomatitis. A detailed description of each study is provided in Tables 3 and 4.

Table 2. Studies excluded in phase 2 and reasons for exclusion (n = 40).

Reference	First author (Year)	Reason for exclusion
1.	Anuradha (2015)	Included
2.	Assareh (2015)	2
3.	Bayraktar (2002)	3
4.	Bayraktar (2004)	7
5.	Bayraktar (2009)	Included
6.	Belazelkovska (2014)	Included
7.	Bibi (2008)	1
8.	Block (2013)	1
9.	Bruzda-Zvviech (2018)	2
10.	Chen (2020)	Included
11.	Chen (2016)	2
12.	Chuang (2005)	2
13.	de Souza (2005)	2 e 3
14.	Eltas (2012)	2
15.	Epstein (1980)	Included
16.	Eraly (2018)	Included
17.	Fragoneze (2016)	3
18.	Honarmand (2017)	Included
19.	Imirzalioglu (2007)	Included
20.	Kaushik (2013)	Included
21.	Kho (1999)	3
22.	Khozeymeh (2016)	Included
23.	Kumar (2020)	3
24.	Marinoski (2019)	Included
25.	Nandan (2005)	7
26.	NCT (2018)	7
27.	Nylund (2015)	2 e 8
28.	Oh (2019)	5
29.	Pallos (2015)	Included
30.	Pereira-Lopes (2019)	2
31.	Pham (2018)	Included
32.	Popovska (2013)	7
33.	Rezaei (2018)	Included
34.	Rumiantsev (2013)	7
35.	Schmalz (2017)	2
36.	Shetty (2018)	Included
37.	Swapna (2018)	2
38.	Temilola (2019)	2
39.	Thorman (2010)	8
40.	Vesterinen (2007)	7

(1) Studies in which patients do not have CRF and do not undergo hemodialysis treatment; (2) Studies that do not have a healthy control group. (3) Patients under 18 years of age; (4) Reviews, case reports, protocols, brief communications, personal opinions, letters, posters, conference abstracts, laboratory research; (5) Studies that do not investigate the association between CRF and salivary diseases; (6) Unpublished studies in the Latin (Roman) and Chinese alphabet; (7) Full text not found; (8) Inadequate statistical analysis for the proposed study.

Risk of bias in included studies and strength of evidence

The risk of bias is summarized in Table 5. The assessment of the certainty of the references and the strength of the evidence was developed by calculating the number of studies that highlighted the presence of a certain number of oral and salivary alterations. None of the articles included met all of the NIH Quality Assessment Tool items. Fifteen articles met at least 8 items. Thus, all articles included in this review met at least 50% of the items obtained (Table 5).

Table 3. Observational data from the studies.

Author/Year	METHODOLOGY	
	Salivary changes	Changes in oral mucosa
Anuradha et al. 2015	Discharge	ND
Bayraktar et al. 2009	Discharge and pH	ND
Belazelkovska et al. 2014	Discharge and pH	Uremic odor, dysgeusia, xerostomia, burning tongue, dry and cracked lips, coated tongue, angular cheilitis, pale mucosa, petechiae/ecchymosis, uremic stomatitis
Chen et al. 2020	pH, urea and ammonia	ND
Epstein et al. 1980	Discharge, urea, total protein, albumin, sodium, chloride, potassium, calcium, phosphate	ND
Eraly et al. 2018	Discharge and pH	ND
Honarmand et al. 2017	Discharge, pH, urea, calcium.	Xerostomia, dysgeusia, gingival bleeding, halitosis, pale mucosa
Imirzalioglu et al. 2007	Discharge, pH, calcium, phosphate	ND
Kaushik et al. 2013	ND	Xerostomia, dysgeusia, bad breath, burning in the tongue, gingival augmentation, petechiae/ecchymosis, gingival bleeding, coated tongue, oral ulcer, potentially malignant lesions, uremic stomatitis
Khozeymeh et al. 2016	Interleukin 6, tumor necrosis factor alpha	ND
Marinoski et al. 2019	Discharge, pH, urea, creatinine, total protein	Pale mucosa, red lesions, petechiae/ecchymosis, white lesions, pigmented lesions, mucosal defects, plaque keratosis, coated tongue, burning tongue, dysgeusia, xerostomia, uremic breath
Pallos et al. 2015	Urea, creatinine, albumin, igA, igG, nitrous oxide, C-reactive protein, pH, total protein	ND
Pham and Le 2017	pH, Discharge, creatine, urea	ND
Rezaei and Mohammadi 2018	Nitrous oxide	ND
Shetty et al. 2018	pH, salivary Discharge	ND
Total	Discharge, pH and urea	Xerostomia, dysgeusia, uremic odor

ND: not described.

Table 4. Epidemiological characteristics of the samples studied in the included articles and research design.

Author/ Year	Study site, country/ State	Study design	(n) participants			Sex n (%)		Average age (years)	
			Study	Control	Total	Study	Control	Study	Control
Anuradha et al. 2015	India, Telangana	Controlled cross-sectional clinical study	24	50	74	ND	ND	ND	ND
Bayraktar et al. 2009	Turkey, Istambul	Controlled cross-sectional clinical study	100	111	211	M=56 (56) F=44 (44)	M=46 (41,4) F=65 (58,6)	46±14	45±18
Belazelkovska et al. 2014	North Macedonia, Skopje	Controlled cross-sectional clinical study	30	20	50	ND	ND	46±14	ND
Chen et al. 2020	China, Taiwan	Controlled longitudinal clinical study	48	24	72	M=21 (56,7) F=27 (43,3)	M=7 (29,2) F=17 (70,8)	58±19	44±9,75
Epstein et al. 1980	USA, New York	Controlled cross-sectional clinical study	9	9	18	M=9 (100)	ND	ND	ND

Table 4. Continued.

Eraly et al. 2018	India, Karnataka	Controlled cross-sectional clinical study	60	20	80	ND	ND	ND	ND
Honarmand et al. 2017	Iran, Zahedan	Controlled cross-sectional clinical study	30	30	60	M=21 (70) F=9(30)	M=21 (70) F=9(30)	38,17±16,88	40,30±18,34
Imirzalioglu et al. 2007	Turkey, Ankara	Controlled cross-sectional clinical study	G1=22 G2=21	G1=22 G2=21	86	G1=(10F+12M) G2=(9F+12M)	G1=(10F+12M) G2=(10F+11M)	49,40±11,95 39,85±14,45	48,4±6,22 38,23±5,02
Kaushik et al. 2013	India, Karnataka	Controlled cross-sectional clinical study	100	25	125	M=61 (61) F=39 (39)	ND	44,3±8,03 44,62±7,53	ND
Khozeymeh et al. 2016	Iran, Isfahan	Controlled cross-sectional clinical study	20	20	40	M=18 (72) F=7(28)	M=16 (64) F=9(36)	54,92±13,60	54,20±12,67
Marinoski et al. 2019	Serbia, Novi Sad	Controlled cross-sectional clinical study	25	25	50	ND	ND	ND	ND
Pallos et al. 2015	Brazil, são Paulo	Controlled cross-sectional clinical study	38	47	85	ND	ND	51,42±12,22	54,76±11,40
Pham and Le 2017	Vietnam, Ho Chi Minh	Controlled cross-sectional clinical study	43	109	152	ND	ND	ND	ND
Rezaei and Mohammadi 2018	Iran, Kermanshah	Controlled cross-sectional clinical study	30	30	60	M=18 (60) F=12 (40)	M=18 (60) F=12 (40)	58,13±9,61	60,77±7,9
Shetty et al. 2018	India, Karnataka	Controlled cross-sectional clinical study	60	20	80	ND	ND	ND	ND
Total	India, Turkey, North Macedonia, China, USA, Iran, Serbia, Brazil, Vietnam	Controlled cross-sectional clinical study	600	563	1.163			50,19	48,95

ND: not described; M: male; F: female.

Description of meta-analysis results

The most common oral changes found in the CRF group, followed by their prevalence, were: mucosal pallor (33.29%), xerostomia (46.36%), gingival bleeding (23.66%), dysgeusia (39.58%) , uremic breath (41.29%), petechiae and ecchymosis (16.58%), coated tongue (25.24%), burning tongue (14%), gingival enlargement (10%), oral ulcer (2%), red spots (16%), white spot keratosis (8%), pigmented spots (4%), mucosal defects (4%), white spots (8%), potentially malignant (3%) and uremic stomatitis (2%). A more detailed description of the results is provided in Table 6.

Regarding the control, the results were: mucosal pallor (4%), xerostomia (13.3%), dysgeusia (9.19%), uremic breath (20%), petechiae and ecchymosis (8%), coated tongue (16%), burning tongue (4%) and red lesions (8%). There were no other oral changes in the healthy group. A more detailed description of the results is provided in Table 7.

The salivary pH in the study group was also more alkaline when compared to the control group. The mean of the study and control groups was (7.52) and (6.98) respectively (Table 8). The salivary flow rate of patients with CRF was, on average, (0.72 mL/min). The systemically healthy group had an average flow of (1.33 mL/min), about 46.6% greater than the study group (Table 9).

Few differences were noted in the salivary composition of the study group. The findings in the CRF group were: sodium (0.0005 mg/mL), potassium (0.0019 mg/mL), calcium (0.0134 mg/mL), phosphate (0.27 mg/mL), interleukin-6 (1.25 x 10^(-8) mg/ml), tumor necrosis factor (9.09 x 10^(-9) mg/ml), urea (0.96 mg/ml), total proteins (1 .75 mg/ml), chloride (0.0012 mg/ml), albumin (0.025 mg/ml), creatinine (0.008 mg/ml) and C-reactive protein (0.55 mg/ml). In the systemically healthy group, the values were: sodium (0.001 mg/mL), potassium (0.0015 mg/mL), calcium (0.019 mg/mL), phosphate (0.14 mg/mL), interleukin-6 (2, 68 x 10^(-9) mg/ml), tumor necrosis factor (3.62 x 10^(-9) mg/ml), urea (0.33 mg/ml), total proteins (1.23 mg /mL), chloride (0.0013 mg/mL), albumin (0.017 mg/mL), creatinine (0.0005 mg/mL) and C-reactive protein (0.2 mg/mL), as described in Table 10 Greater amounts of IgG and IgA were also found in patients with CRF.

Table 6. Detailed results of the meta-analysis regarding oral lesions in the CRF group.

Meta-analysis (number of cases included)	Cases	Total	Prevalence (95% CI)	I^2 (95% CI)	Forecast interval
Oral amendments (CRF)					
Mucosal pallor (n=2)	18	55	33.29% (20.09-49.76%)	32% (NE)	NE
Xerostomia (n=3)	69	155	46.36% (35.72-57.35%)	37% (0-80%)	1.24-98.35%
Gingival bleeding (n=2)	30	130	23.66% (17.15-31.69)	0% (NE)	NE
Dysgeusia (n=3)	59	150	39.58% (32.13-47.55%)	0% (0-72%)	7.39-84.33%
Uremic breath (n=3)	65	155	41.29% (28.32-55.59%)	56% (0-87%)	0.14-99.71%
Petechiae and bruises (n=2)	20	125	16.58% (10.40-25.40%)	9% (NE)	NE
Coated tongue (n=2)	31	125	25.24% (18.44-33.51%)	0% (NE)	NE
*Burning tongue (n=1)**	14	100	14% (NR)	NR	NR
*Gingival augmentum (n=1)**	10	100	10% (NR)	NR	NR
*Oral ulcer (n=1)**	2	100	2% (NR)	NR	NR
*Red lesions (n=1)**	4	25	16% (NR)	NR	NR
*White spot keratosis (n=1)**	2	25	8% (NR)	NR	NR
*Pigmented lesions (n=1)**	1	25	4% (NR)	NR	NR
*Mucosal defects (n=1)**	1	25	4% (NR)	NR	NR
*White lesions (n=1)**	2	25	8% (NR)	NR	NR
*Potentially malignant lesions (n=1)**	3	100	3% (NR)	NR	NR
*Uremic stomatitis (n=1)**	2	100	2% (NR)	NR	NR

*(n=1) only one study; NR: unreported; NE: not estimated.

Table 7. Detailed results of the meta-analysis of oral lesions of the control group.

Meta-analysis (number of cases included)	Cases	Total	Prevalence (95% CI)	I^2 (95% CI)	Forecast interval
Oral changes (control)					
*Mucosal pallor (n=1)**	1	25	4% (NR)	NR	NR
*Xerostomia (n=1)**	4	30	13,3% (NR)	NR	NR
Dysgeusia (n=2)	4	55	9.19% (3.87-20.29%)	0% (0-72%)	NE
*Uremic breath (n=1)**	6	30	20% (NR)	NR	NR
*Petechiae and bruises (n=1)**	2	25	8% (NR)	NR	NR
*Coated tongue (n=1)**	4	25	16% (NR)	NR	NR
*Burning tongue (n=1)**	1	25	4% (NR)	NR	NR
*Red lesions (n=1)**	2	25	8% (NR)	NR	NR

*(n=1): only one study; NR: unreported; NE: not estimated; Control: systemically healthy individuals.

Table 5. Quality assessment of the studies included according to the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

QUESTION	ANURADHA et al. 2015	BAYRAKTAR et al. 2009	BELAZELKOVSKA et al. 2014	CHEN et al. 2020	EPSTEIN et al. 1980	ERALY et al. 2018	HONARMAND et al. 2017	IMIRZALIOGLU et al. 2007	KAUSHIK et al. 2013	KHOZEYMEH et al. 2016	MARINOSKI et al. 2019	PALLOS et al. 2015	PHAM and LE 2017	REZAEI and MOHAMMADI 2018	SHETTY et al. 2018	TOTAL
1. Research question.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
2. Study population.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
3. Rate of participants of eligible persons.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
4. Eligibility criteria.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
5. Sample size.	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	2
6. Exposure evaluation.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
7. Term.	NA	NA	NA	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1
8. Exposure levels.	NA	NA	Yes	Yes	NA	Yes	NA	Yes	NA	NA	NA	NA	NA	NA	Yes	5
9. Exposure measures.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
10.Repeated exposure assessment.	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1
11. Results measures.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
12.Blinding aides.	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0
13. Follow-up fee.	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	0
14.Statistical analyses.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
TOTAL	8	8	9	12	8	9	8	9	8	8	9	9	8	8	9	

Table 8. Mean salivary pH of the CRF versus control group.

Author/year	N total	CRF Group	Control group
Anuradha et al. 2015	74	NR	NR
Bayraktar et al. 2009	211	8,12	7,16
Belazelkovska et al. 2014	50	6,91	6,78
Chen et al. 2020	72	7,80	7,00
Epstein et al. 1980	18	NR	NR
Eraly et al. 2018	80	7,01	6,65
Honarmand et al. 2017	60	8,41	7,01
Imirzalioglu et al. 2007	86	7,94	7,6
Kaushik et al. 2013	125	7,26	6,92
Khozeymeh et al. 2016	40	NR	NR
Marinoski et al. 2019	50	6,88	6,52
Pallos et al. 2015	85	7,76	8,22
Pham and Le 2017	152	7,80	7,00
Rezaei and Mohammadi 2018	60	NR	NR
Shetty et al. 2018	80	6,83	6,00
Average		7,52	6,98

CRF: chronic renal failure; Control: systemically healthy; NR: unreported; pH: hydrogenionic potential.

Table 9. Mean salivary discharge of the CRF versus control group.

Author/year	Total	CRF Group (mL/min)	Control group (mL/min)
Anuradha et al. 2015	74	0,41	0,68
Bayraktar et al. 2009	211	0,70	1,64
Belazelkovska et al. 2014	50	0,31	0,54
Chen et al. 2020	72	0,59	1,90
Epstein et al. 1980	18	NR	NR
Eraly et al. 2018	80	0,35	0,72
Honarmand et al. 2017	60	1,02	1,46
Imirzalioglu et al. 2007	86	1,63	2,44
Kaushik et al. 2013	125	0,48	1,42
Khozeymeh et al. 2016	40	NR	NR
Marinoski et al. 2019	50	0,30	0,51
Pallos et al. 2015	85	NR	NR
Pham and Le 2017	152	1,25	1,54
Rezaei and Mohammadi 2018	60	NR	NR
Shetty et al. 2018	80	0,87	1,80
Average	1.243	0,72	1,33

CRF: chronic renal failure; Control: systemically healthy; NR: unreported; n: number of studies included; mg: milligrams; mL: milliliters.

4. Discussion

After conducting this research, it was noted that the hypothesis of this study was confirmed, since patients with CRF undergoing hemodialysis treatment present differences in salivary composition/quantity, as well as with regard to the prevalence of oral lesions, when compared to healthy control subjects. This finding is consistent with the literature (Akar et al. 2011; Pham and Le 2019), which states that the fluid restriction and side effects of drug therapy (constant use of diuretics), commonly causes individuals with CRF to have changes in the oral cavity such as xerostomia. Therefore, insufficient salivary flow results in factors, such as reduced bolus preparation, reduced taste, and increased susceptibility of oral structures to disease (Pham and Le 2019).

Table 10. Detailed average of the results found in the salivary composition of individuals with CRF and those systemically healthy.

Meta-analysis (number of studies included)	Individuals with CRF		Systemically healthy individuals	
	Total	Mean (mg/mL)	Total	Mean (mg/mL)
*Sodium(n=1)**	9	0,0005	9	0,0010
*Potassium (n=1)**	9	0,0019	9	0,0015
Calcium (n=3)	82	0,0130	82	0,0190

Table 10. Continued.

Phosphate (n=2)	52	0,2700	52	0,1400
*Interleuin 6 (n=1)**	20	1,25 x 10^(-8)	20	2,68 x 10^(-9)
*Tumor necrosis factor (n=1)**	20	9,09 x 10^(-9)	20	3,62 x 10^(-9)
Urea (n=4)	146	0,9600	197	0,3300
Total proteins (n=3)	72	1,7500	81	1,2300
*Chloride (n=1)**	9	0,0012	9	0,0013
*Albumin (n=1)**	9	0,0250	9	0,0170
*Creatinine (n=1)**	25	0,0080	25	0,0005
*C-reactive protein (n=1)**	25	0,5500	25	0,2000

*(n=1) only one study; CRF: chronic renal failure; NR: Not reported; n: number of studies included; mg: milligrams; mL: milliliters.

The countries that published the most studies in relation to the research question addressed were: India, Turkey, Northern Macedonia, China, United States of America, Iran, Serbia, Brazil and Vietnam. However, this does not mean that in these countries there is a greater occurrence of individuals with CRF. In fact, this data demonstrates which countries invest the most in the diagnosis and early treatment of CRF, associating it with the oral health of individuals (Crews et al. 2019).

The average age of participants with CRF was 50.19 years, demonstrating that this is a disease that mainly affects older individuals. It was also found that this condition affects males to a greater extent, as was found in previous studies (Aguiar et al. 2020). However, European studies have shown a higher prevalence of CRF in women than in men (Cepoi et al. 2012). A previous study in the state of Paraná/Brazil also identified a higher prevalence of CRF in female individuals. Such differences in results regarding gender encourage reflection on the possibility of genetic and geographic interference in the incidence of CRF in different populations, since individuals in the southern region of Brazil are mostly Caucasians and descendants of European colonizers. Other studies have also pointed out the association of two genetic variants as influencers of nephropathy in African descendants (Kao et al. 2008; Peralta et al. 2011). As a result, the need for a survey of the incidence of CRF in all regions of the country is evident, as each region of Brazil is composed of different ethnic groups. In this way, it would be possible to identify the characteristics of the macro-regions, helping in the planning of measures for the treatment and prevention of CRF, prioritizing the peculiarities of each geographic location.

According to the results obtained in the evaluated studies, systemically healthy individuals had a much smaller amount of oral lesions when compared to the group of patients with CRF. However, no lesion showed a significant prevalence to the point of being considered a specific characteristic of patients with CRF (pathognomonic lesion). Furthermore, there are few studies comparing the prevalence of oral alterations in these patients, preventing a more solid knowledge of their stomatognathic problems and their oral needs. The predominant oral lesions in individuals with CRF, according to the studies included in the research, were: pale mucosa, xerostomia, gingival bleeding, dysgeusia, uremic breath and coated tongue (Block et al. 2013; Kaushik et al. 2013; Belazelkovska et al. 2014; Marinoski et al. 2019).

Xerostomia is one of the problems most commonly presented in all patients with CRF because it is a consequence of hyposalivation, consumption of medications and also low fluid intake - the latter is part of the medical recommendations for individuals with CRF to maintain a water balance in the organism (Epstein et al. 1980). Mucosal pallor, on the other hand, is portrayed in the literature as a consequence of the anemic condition and the low production of erythropoietin (a glycoprotein that controls the production of red blood cells) in individuals with CRF (Anuradha et al. 2015). Gingival bleeding in these individuals is related to the increased occurrence of gingivitis and periodontitis. This bleeding, in addition to being a consequence of inefficient oral hygiene, is also associated in the literature with a dysregulation of the serum calcium-phosphate product, factors that contribute to the formation of dental calculus (Antoniades et al. 2006). The uremic breath present in most patients is justified in the literature as a consequence of the high presence of urea in saliva (Kho et al. 1999).

The mean salivary flow in individuals with CRF was significantly lower than in the control group and was similar to the values reported by previous studies (Pereira-Lopes et al. 2019; Kumar et al. 2020). These results justify the findings related to dysgeusia and the greater occurrence of lesions in these individuals, since the reduction in salivary flow causes a reduction in the preparation of the bolus, a reduction in taste, and an increase in the susceptibility of oral structures to diseases. On the other hand, none of the studies

included in the review evaluated the relationship between medications used by patients and their connection with the reduction in salivary flow, as was done in the study by Miguel et al. (2006), where from the assessment of medical records, it was identified that each patient on hemodialysis was using at least one medication that negatively interfered with salivary flow, such as antihypertensives and antidepressants. In addition, the studies should have collected both stimulated and non-stimulated saliva, and most studies chose only one or the other, when in fact the analysis of both forms would leave the data and the possibilities of comparison more complete.

The amount of urea, phosphate, total protein, creatinine and C-reactive protein was slightly higher in patients with CRF. However, there was no significant difference in the other salivary components when compared to the healthy control group. Furthermore, as there are few studies that assess such salivary characteristics, it is unsustainable to treat such findings as pathognomonic of individuals with CRF (Kaushik et al. 2013; Rumiantsev et al. 2013; Pallos et al. 2015; Shetty, Hegde and Eraly, 2018; Marinoski et al. 2019; Kumar et al. 2020).

The mean values of salivary pH in the study group also had differences when compared to the control group. The saliva of the study group was more alkaline, but still within the acceptable range. The salivary alkalinity in these individuals is due to the greater amount of urea present in the saliva, which is degraded and transformed into ammonia, consequently raising the salivary pH (Wong et al. 2012; Rodrigues et al. 2020; Rodrigues et al. 2021). Due to the alkalinity of saliva, it reduces the deterioration capacity of the organic matter present in the oral environment, favoring the formation of tartar and therefore the presence of periodontal disease. Furthermore, the presence of periodontal disease in these individuals increases the amount of systemic inflammation, consequently raising the values of C-reactive protein and interleukins (Craig et al. 2013). The phosphate concentration in the saliva of CRF patients is also higher due to the low salivary flow, since phosphate is inversely proportional to the salivary flow rate. Furthermore, this phosphataemia can often contribute to the development of hyperparathyroidism in individuals on hemodialysis (Epstein et al. 1980).

The small number of dental studies in patients with CRF limits the description of a pattern of oral conditions in these individuals, preventing it from being able to draw a concrete relationship between oral alterations and hemodialysis treatment. Thus, it is relevant that new clinical studies be carried out on this population and that we seek to know more about the needs of these patients, since the number of individuals with CRF has grown worldwide. It is also worth remembering that the dentist plays a fundamental role in the prevention and treatment of oral diseases and that hospital dentistry has proven to be a very important science for the treatment of systemic diseases with oral implications (Wong et al. 2012).

5. Conclusions

Individuals with chronic renal failure undergoing hemodialysis treatment are more prone to changes in both the quantity and quality of saliva, as well as having a greater number of lesions/oral alterations. However, there are still few studies on this topic and it is not possible to reach a solid conclusion about which are the most prevalent alterations and can be considered characteristics of these individuals. Thus, there is a need for more clinical studies in patients with CRF, as this is a population that is little explored within the dental field.

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References

AGUIAR, L.K., et al. Fatores associados à doença renal crônica: Inquérito epidemiológico da Pesquisa Nacional de Saúde. *Revista brasileira de epidemiologia*. 2020, **23**, E200044. https://doi.org/10.1590/1980-549720200044

AKAR, H., et al. Systemic consequences of poor oral health in chronic kidney disease patients. *Clinical Journal of the American Society of Nephrology.* 2011, **6**, 218-226. https://doi.org/10.2215/cjn.05470610

ANTONIADES, D.Z., et al. Ulcerative uremic stomatitis associated with untreated chronic renal failure: Report of a case and review of the literature. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2006, **101**, 608-613. https://doi.org/10.1016/j.tripleo.2005.08.006

ANURADHA, B. R., et al. Oral and salivary changes in patients with chronic kidney disease: A clinical and biochemical study. *Journal of indian society of periodontology*. 2015, **19**, 297-301. https://doi.org/10.4103/0972-124x.154178

ASSAREH, A. A., et al. No relationship between serumand salivary β2- microglobulin levels in a sample of adult diabetic men with chronic kidney disease without renal replacement therapy. *Cell journal*. 2014, **16**, 179-186

BARRETO, S. M., et al. Chronic kidney disease among adult participants of the ELSA-Brasil cohort: Association with race and socioeconomic position. *Journal of epidemiology and community health.* 2016, **70**, 380-389. https://doi.org/10.1136/jech-2015-205834

BAYRAKTAR, G., et al. Stimulated salivary flow rate in chronic hemodialysis patients. *Nephron*. 2002, **91**, 210-214. https://doi.org/10.1159/000058394

BAYRAKTAR, G., et al. Evaluation of salivary parameters and dental status in adult hemodialysis patients. *Clinical nephrology*. 2004, **62**, 380-383. https://doi.org/10.5414/cnp62380

BAYRAKTAR, G., et al. Oral health and inflammation in patients with end-stage renal failure. *Peritoneal dialysis international*. 2009, **29**, 472-479
BELAZELKOVSKA, A., et al. Oral and salivary changes in patients with chronic kidney disease. *BANTAO journal*. 2014, **12**, 97-102. https://doi.org/10.2478/bj-2014-0019

BIBI, G., GREEN, Y. and NAGLER, R. M. Compositional and oxidative analysis in the saliva and serum of predialysis chronic kidney disease patients and end-stage renal failure patients on peritoneal dialysis. *Therapeutic apheresis and dialysis*. 2008, **12**, 164-170. https://doi.org/10.1111/j.1744-9987.2008.00564.x

BLOCK, G. A., et al. Effect of salivary phosphate-binding chewing gum on serum phosphate in chronic kidney disease. *Nephron clinical practice*. 2013, **123**, 93-101. https://doi.org/10.1159/000351850

BRUZDA-ZWIECH, A., SZCZEPANSKA, J. and ZWIECH, R. Xerostomia, thirst, sodium gradient and inter-dialytic weight gain in hemodialysis diabetic vs. non-diabetic patients. *Medicina oral, patologia oral y cirugia bucal*. 2018, **23**, e406-e412. https://doi.org/10.3290/j.qi.a4192010.4317/medoral.22294

CEPOI, V., et al. The prevalence of chronic kidney disease in the general population in Romania: A study on 60,000 persons. *International urology and nephrology*. 2012, **44**, 213-220. https://doi.org/10.1007/s11255-011-9923-z

CHEN, W., et al. Biochemical pathways of breath ammonia (NH3) generation in patients with end-stage renal disease undergoing hemodialysis. *Journal of breath research*. 2016, **10**, 036011. https://doi.org/10.1088/1752-7155/10/3/036011

CHEN, C. C., et al. Correlation between breath ammonia and blood urea nitrogen levels in chronic kidney disease and dialysis patients. *Journal of breath research*. 2020, **14**, 036002. https://doi.org/10.1088/1752-7163/ab728b

CHUANG, S. F., et al. Oral and dental manifestations in diabetic and nondiabetic uremic patients receiving hemodialysis. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*. 2005, **99**, 689-695. https://doi.org/10.1016/j.tripleo.2004.06.078

CRAIG, R. G., et al. Periodontal diseases and systemic inflammation. *Seminars in dialysis*. 2013, **26**, 23-28. http://doi.org/10.1111/sdi.12022

CREWS, D. C., BELLO, A. K. and SAADI, G. 2019 World kidney day editorial - Burden, access, and disparities in kidney disease. *Brazilian journal of nephrology*. 2019, **41**, 1-9. https://doi.org/10.1590/2175-8239-JBN-2018-0224

DE SOUZA, C. R., et al. L. Assessment of periodontal condition of kidney patients in hemodialysis. *Journal of the brazilian medical association*. 2005, **51**, 285-289. https://doi.org/10.1590/s0104-42302005000500021

ELTAS, A., et al. Assessment of oral health in peritoneal dialysis patients with and without diabetes mellitus. *Peritoneal dialysis international*. 2012, **32**, 81-85. https://doi.org/10.3747/pdi.2010.00113

EPSTEIN, S. R., MANDEL, I. and SCOPP, I. W. Salivary composition and calculus formation in patients undergoing hemodialysis. *Journal of periodontology*. 1980, **51**, 336-338. https://doi.org/10.1902/jop.1980.51.6.336

ERALY, S. M., et al. Evaluation of salivary parameters and oral health status in adult hemodialysis patients. *Research journal of pharmaceutical biological and chemical sciences*. 2018, **9**, 1468-1475.

HIGGINS, J. P. T. and GREEN, S. Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]. *The cochrane collaboration*, 2011.

HILL, N. R., et al. Global prevalence of chronic kidney disease - A systematic review and meta-analysis. *PloS one.* 2016, **11**, e0158765. https://doi.org/10.1371/journal.pone.0158765

HONARMAND, M., et al. Oral manifestation and salivary changes in renal patients undergoing hemodialysis. *Journal of clinical and experimental dentistry*. 2017, **9**, e207-e210. https://doi.org/10.4317/jced.53215

IMIRZALIOGLU, P., et al. Dental erosion in chronic renal failure. *Clinical oral investigations*. 2007, **11**, 175-180. https://doi.org/10.1007/s00784-007-0100-9

JONES, D. J. W., et al. Latent learning in end stage renal disease (ESRD). *Physiology & behavior*. 2015, **142**, 42-47. https://doi.org/10.1016/j.physbeh.2015.01.033

KAO, W. H. L., et al. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. *Nature Genetics*. 2008, **40**, 1185-1192. https://doi.org/10.1038/ng.232

KAUSHIK, A., et al. Oral and salivary changes among renal patients undergoing hemodialysis: A cross-sectional study. *Indian journal of nephrology*. 2013, **23**, 125-129. https://doi.org/10.4103/0971-4065.109421

KENNEDY, C. E. et al. The Evidence Project risk of bias tool: assessing study rigor for both randomized and non-randomized intervention studies. *Systematic Reviews*. 2019, **8**, 3. https://doi.org/10.1186/s13643-018-0925-0

KHO, H. S., et al. Oral manifestations and salivary flow rate, pH, and buffer capacity in patients with end-stage renal disease undergoing hemodialysis. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*. 1999, **88**, 316-319. https://doi.org/10.1016/s1079-2104(99)70035-1

KHOZEYMEH, F., et al. Salivary levels of interleukin-6 and tumor necrosis factor-α in patients undergoing hemodialysis. *Dental research journal*. 2016, **13**, 69-73. https://doi.org/10.4103/1735-3327.174720

KITAMURA, M., et al. Pathological characteristics of periodontal disease in patients with chronic kidney disease and kidney transplantation. *International journal of molecular sciences*. 2019, **20**, 3413. https://doi.org/10.3390/ijms20143413

KUMAR, T., et al. Evaluation of salivary flow rate, pH, and buffer capacities in end-stage renal disease patients versus control - A prospective comparative study. *Journal of family medicine and primary care.* 2020, **9**, 2985-2989. https://doi.org/10.4103/jfmpc.jfmpc_242_20

LIU, Z. H. Nephrology in china. *Nature reviews nephrology.* 2013, **9**, 523-528. https://doi.org/10.1038/nrneph.2013.146

MARINOSKI, J., et al. Oral mucosa and salivary findings in non-diabetic patients with chronic kidney disease. *BMC nephrology*. 2019, **102**, 205-211. https://doi.org/10.1186/s12882-019-1546-010.1016/j.archoralbio.2019.04.021

MIGUEL, L. C. M., LOCKS, A. and NEUMANN, V. Redução do fluxo salivar em hemodialisados. *Brazilian journal of nephrology*. 2006, **28**, 20-24.

MURPHY, S. W. Longitudinal Studies 1: Determinants of Risk. *Methods in Molecular Biology*. 2021, **2249**, 83-101. https://doi.org/10.1007/978-1-0716-1138-8_6

NANDAN, R. K., SIVAPATHASUNDHARAM, B. and SIVAKUMAR, G. Oral manifestations and analysis of salivary and blood urea levels of patients under going hemodialysis and kidney transplant. *Indian journal of dental research*. 2005, **16**, 77-82.

NCT, 2018. Effects of photobiomodulation in salivary analysis of chronic renal failure patients. Available from: https://clinicaltrialsgov/show/NCT03647813

NATIONAL HEARTH, LUNG, AND BLOOD INSTITUTE – NIH. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. NHLBI, NIH, 2017. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort

NYLUND, K. M., et al. Periodontal inflammatory burden and salivary matrix metalloproteinase-8 concentration among patients with chronic kidney disease at the predialysis stage. *Journal of periodontology*. 2015, **86**, 1212-1220. https://doi.org/10.1902/jop.2015.150285

OH, M. Y. and CHO, M. K. Effects of gargling with an aroma solution on xerostomia, halitosis, and salivary pH in hemodialysis patients, A randomized controlled trial. *The open nursing journal*. 2019, **13**, 1-9. https://doi.org/10.2174/1874434601913010001

PAGE, M. J, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research ed.)*. 2021, **372**. https://doi.org/10.1136/bmj.n71

PALLOS, D., et al. Salivary markers in patients with chronic renal failure. *Archives of oral biology*. 2015, **60**, 1784-1788. https://doi.org/10.1016/j.archoralbio.2015.09.008

PERALTA, C. A., et al. Racial and ethnic differences in kidney function decline among persons without chronic kidney disease. *Journal of the american society of nephrology*. 2011, **22**, 1327-1334. https://doi.org/10.1681/asn.2010090960

PEREIRA-LOPES, O., et al. Influence of dialysis therapies on oral health: A pilot study. *Quintessence international*. 2019, **50**, 216-223. https://doi.org/10.3290/j.qi.a41920

PHAM, T. A. V. and LE, D. D. Dental condition and salivary characteristics in vietnamese patients with chronic kidney disease. *International journal of dental hygiene*. 2019, **17**, 253-260. https://doi.org/10.1111/idh.12380

POPOVSKA, M., et al. Oral findings in end-stage renal disease. *Prilozi*. 2013, **34**, 85-91.

QUEIROZ, S. M. A., et al. Influence of dialysis duration and parathyroid hormone on the clinical and radiographic oral conditions of pre-transplant patients with chronic kidney disease. *Brazilian journal of oral sciences*. 2013, **12**, 125. https://doi.org/10.1590/S1677-32252013000200011

REZAEI, F. and MOHAMMADI, R. Comparison of saliva nitric oxide between chronic kidney disease before and after dialysis and with control group. *The open dentistry journal*. 2018, **12**, 213-218. https://doi.org/10.2174/1874210601812010213

RODRIGUES, R.P.C.B., et al. Saliva as an alternative to blood in the determination of uremic state in adult patients with chronic kidney disease: A systematic review and meta-analysis. *Clinical Oral Investigations*. 2020, **24**, 2203-2217. https://doi.org/10.1007/s00784-020-03340-2

RODRIGUES, R. P. C. B., et al. Saliva as a tool for monitoring hemodialysis: A systematic review and meta-analysis. *Brazilian Oral Research*. 2020, **35**, e016. https://doi.org/10.1590/1807-3107bor-2021.vol35.0016

RODRIGUES, R. P. C. B., et al. Salivary changes in chronic kidney disease and in patients undergoing hemodialysis: A systematic review and meta-analysis. *Journal of Nephrology*. 2022, **35**, 1339-1367. https://doi.org/10.1007/s40620-022-01274-4

RUMIANTSEV, V. A., et al. Impairment of oral cavity acid-base balance in patients with concomitant somatic diseases. *Stomatologiia*. 2013, **92**, 22-26.

SCHMALZ, G., et al. Dental and periodontal health, and microbiological and salivary conditions in patients with or without diabetes undergoing haemodialysis. *International dental journal*. 2017, **67**, 186-193. https://doi.org./10.1111/idj.12282

SHETTY, P., HEGDE, M. N. and ERALY, S. M. Evaluation of salivary parameters and dental status in adult hemodialysis patients in an indian population. *Journal of clinical and experimental dentistry*. 2018, **10**, e419-e424. https://doi.org/10.4317/jced.54633

SOUZA, B. D. M. et al. Incidence of root resorption after concussion, subluxation, lateral luxation, intrusion, and extrusion: a systematic review. *Clinical oral investigations*. 2020, **24**, 1101-1111. https://doi.org/10.1007/s00784-020-03199-3.

SWAPNA, L. A., KOPPOLU, P. and PRINCE, J. Oral health in diabetic and nondiabetic patients with chronic kidney disease. *Saudi journal of kidney diseases and transplantation*. 2017, **28**, 1099-1105. https://doi.org/10.4103/1319-2442.215123

TEMILOLA, D. O., et al. Salivary creatinine as a diagnostic tool for evaluating patients with chronic kidney disease. *BMC Nephrology*. 2019, **20**, 387. https://doi.org/10.1186/s12882-019-1546-0

THORMAN, R., et al. Inflammatory cytokines in saliva: Early signs of metabolic disorders in chronic kidney disease. A controlled cross-sectional study. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*. 2010, **110**, 597-604. https://doi.org/10.1016/j.tripleo.2010.07.007

VESTERINEN, M., et al. Oral health and dental treatment of patients with renal disease. *Quintessence international*. 2007, **38**, 211-219.

WADDINGTON, H. et al. Quasi-experimental study designs series-paper 6: risk of bias assessment. *Journal of Clinical Epidemiology*. 2017, **89**, 43-52. https://doi.org/10.1016/j.jclinepi.2017.02.015.

WONG, C. J., et al. CKiD (CKD in children) prospective cohort study: A review of current findings. *American Journal of Kidney Diseases*. 2012, **60**, 1002-1011. https://doi.org/10.1053/j.ajkd.2012.07.018

YAMASHITA, J. M., et al. Manifestações bucais em pacientes portadores de Diabetes Mellitus: Uma revisão sistemática. *Revista de odontologia da UNESP*. 2013, **42**, 211-220.

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