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SYSTEMATIC REVIEWS

Salivary changes in chronic kidney disease and in patients undergoing hemodialysis: a systematic review and meta-analysis

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Abstract

Objectives This study is aimed at describing changes in salivary flow rate and ionic composition present in the saliva of chronic kidney disease (CKD) patients by assessing the pH, calcium, phosphate, and phosphorus concentrations and comparing them to healthy individuals, along with exploring the influence of hemodialysis on these parameters.

Methods The bibliographical search was performed in nine databases to find all types of studies, including observational clinical studies, without restrictions regarding publication year or language. Two reviewers selected the studies, extracted the data, and assessed the risk of bias using JBI tools. Random-effect meta-analysis was performed with the standardized mean difference (SMD) as effect estimate, at a 95% confidence interval.

Results Thirty-three studies were included in the qualitative synthesis and 31 studies were included in the meta-analysis. Chronic kidney disease patients presented lower salivary flow rate (SMD: − 1.73; 95% CI = − 2.14; − 1.31), higher pH (SMD: 1.57; 95% CI = 1.11; 2.03), and higher phosphorus concentration (SMD: 0.86; 95% CI = 0.63; 1.09) in saliva. Concurrently, salivary flow rate and pH presented significant changes after hemodialysis, with higher salivary flow rate (SMD: 0.53; 95% CI = 0.25; 0.81) and lower pH (SMD: − 0.53; 95% CI = − 0.88; − 0.19) in patients on hemodialysis treatment.

Conclusion Chronic kidney disease patients present reduced salivary flow rate and increased pH and phosphorus concentration in saliva. Hemodialysis can increase the salivary flow rate of these patients.

Keywords Salivary composition · Chronic kidney disease · Salivary flow rate · Saliva

Introduction

Chronic kidney disease (CKD), a chronic structural and functional degeneration of the kidneys [1], has a worldwide prevalence between 11 and 13% [2] and it is considered a global health problem, representing a major morbidity and mortality factor in non-communicable chronic diseases [3, 4]. According to the Glomerular Filtration Rate (GFR) and the degree of proteinuria (albumin/creatinine ratio) [1] CKD severity can be classified into various stages.

End-stage renal disease patients require therapies that restore renal function [5], such as dialysis treatments

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(hemodialysis and peritoneal dialysis) and kidney transplant [1]. Hemodialysis is the most used [6], and it focuses both on filtering plasma electrolytes at high concentrations, especially hypocalcemia and metabolic acidosis [7], and on normalizing the circulatory volume by eliminating excess fluids from the organism [5].

About 90% of CKD patients have oral signs and symptoms [8, 9] such as xerostomia, halitosis, metallic taste, uremic stomatitis, mucositis, glossitis, among others [10–12]. Additionally, CKD patients often have changes in salivary flow rate and composition [13, 14].

CKD patients usually have a lower salivary flow rate [10], and their saliva has higher concentrations of urea, sodium, phosphate, thiocyanate, and potassium; reduced calcium levels; increased pH; and decreased buffering capacity [6, 15–17] in comparison to healthy individuals. Altogether, these salivary changes lead to oral dysfunctions in the remineralization process [18], and to the formation of dental calculus, which can ultimately influence the occurrence of dental caries and periodontal diseases, respectively [19, 20]. Understanding the impact of CKD in the salivary flow rate, pH, and ionic composition can be relevant for dental treatment planning, as it can assist in establishing diagnoses, medication prescriptions, and adequate oral health instructions tailored to CKD patients [9, 21].

It is of the utmost importance to provide high-quality evidence about the relationship between CKD and salivary changes in patients diagnosed with the disease and undergoing hemodialysis, as well as to verify the action of the dialytic treatment in the saliva of these patients right after the procedure. Thus, the present systematic review aims to assess changes in the flow rate, pH, and levels of calcium, phosphate, and phosphorus in the saliva of CKD patients and to investigate the influence of hemodialysis on these parameters.

Materials and methods

Protocol registration

The protocol utilized in this systematic review was described according to the PRISMA-P guidelines (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [22] and registered in the PROSPERO database under number CRD42021231129. This systematic review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) guidelines [23] and performed according to the norms of the JBI manual for Evidence Synthesis [24].

Research question and eligibility criteria

This review aimed to answer two guiding questions, which were designed according to the PECO acronym (Population, Exposure, Comparator, and Outcome): (1) “Will end-stage chronic kidney disease patients undergoing hemodialysis present changes in salivary flow rate, pH, and levels of calcium, phosphate, and phosphorus when compared to healthy individuals?” and (2) “Can a single hemodialysis session change the salivary flow rate, pH, and levels of phosphate, phosphorus, and calcium the in saliva of CKD patients?”.

Inclusion criteria

Question 1:

- Population: Adults (> 18 years old);
- Exposure: Chronic kidney disease and hemodialysis (GFR < 15 ml/min/1.73 m^2);
- Control group: Healthy individuals;
- Outcome: Salivary flow rate, pH, and levels of phosphate, phosphorus, and calcium in whole saliva;
- Study design: Observational studies (case–control or controlled cross-sectional).

Question 2:

- Population: Adult patients (> 18 years old) with chronic kidney disease;
- Exposure: Hemodialysis (GFR < 15 ml/min/1.73 m^2);
- Control Group: Salivary parameters (flow rate, pH, and levels of phosphate and calcium) before dialysis;
- Outcome: Salivary flow rate, pH, and levels of phosphate, phosphorus, and calcium after dialysis;
- Study design: Pre/post-test studies with or without a control group with healthy participants.

There were no restrictions of publication language or year to any of the guiding questions.

Exclusion criteria

- Literature reviews, letters to the editor/editorials, personal opinions, books/book chapters, case reports/case series, pilot studies, conference abstracts, and patents;
- Studies with overlapping results/samples;
- Studies with pediatric patients;
- Studies that did not collect whole saliva;
- Studies including patients with renal diseases other than CKD.

Sources of information and search

Electronic searches were performed in MedLine (via PubMed), Scopus, LILACS, SciELO, Web of Science, Embase, and LIVIVO databases. OpenThesis and OpenGrey databases were used to partially capture the "grey literature". MedLine search was updated constantly by PubMed through warnings, until July 2021. MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors), and Emtree (Embase Subject Headings) resources were used to select the search descriptors. Moreover, synonyms and free words composed the search. The Boolean operators "AND" and "OR" were used to improve the research strategy with several combinations. The search strategies in each database were made according to their respective syntax rules (Table 1). The results obtained in the primary databases were initially exported to EndNote Web™ software (Thomson Reuters, Toronto, Canada) for cataloging and for the removal of duplicates. "Grey literature" results were exported to Microsoft Word (Microsoft™, Ltd, Washington, USA) for the removal of duplicates.

Study selection

Before selecting the studies, the reviewers discussed the eligibility criteria and applied them to a sample of 20% of the studies retrieved to determine the inter-examiner agreement. After reaching a Kappa $\geq$ 0.81, the reviewers (MTCV and RCPBR) performed a title analysis of the studies (first phase), and those not related to the topic were eliminated. In

Table 1 Strategies for database search

Database	Search strategy (July, 2020) and update (until July, 2021)
Main databases	
Embase https://www.embase.com	('kidney diseases'/exp OR 'kidney diseases' OR 'kidney disease'/exp OR 'kidney disease' OR 'chronic kidney disease'/exp OR 'chronic kidney disease' OR 'chronic renal disease'/exp OR 'chronic renal disease' OR 'renal insufficiencies' OR 'kidney insufficiency'/exp OR 'kidney insufficiency' OR 'renal dysfunction'/exp OR 'renal dysfunction' OR 'kidney dysfunction'/exp OR 'kidney dysfunction' OR 'renal failure'/exp OR 'renal failure' OR 'renal injury'/exp OR 'renal injury') AND ('saliva'/exp OR 'saliva' OR 'salivary changes' OR 'salivary flow'/exp OR 'salivary flow' OR 'salivary ph'/exp OR 'salivary ph' OR 'salivary viscosity' OR 'salivary phosphate' OR 'salivary calcium' OR 'salivary volume' OR 'salivary composition')
LILACS http://lilacs.bvsalud.org/	("Kidney Diseases" OR Chronic Kidney Disease" OR "Kidney Insufficiency" OR "Kidney Dysfunction" OR "Renal Failure") AND ("Saliva" OR "Salivary Changes")
LIVIVO https://www.livivo.de/	(("Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" OR "Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Dysfunction" OR "Kidney Dysfunction" OR "Renal Failure" OR "Renal Injury") AND ("Saliva" OR "Salivary Changes" OR "Salivary Flow" OR "Salivary pH" OR "Salivary Viscosity" OR "Salivary Phosphate" OR "Salivary Calcium" OR "Salivary Volume" OR "Salivary Composition"))
PubMed http://www.ncbi.nlm.nih.gov/pubmed	(("Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" OR "Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Dysfunction" OR "Kidney Dysfunction" OR "Renal Failure" OR "Renal Injury") AND ("Saliva" OR "Salivary Changes" OR "Salivary Flow" OR "Salivary pH" OR "Salivary Viscosity" OR "Salivary Phosphate" OR "Salivary Calcium" OR "Salivary Volume" OR "Salivary Composition"))
SciELO https://scielo.org/	("Kidney Diseases" OR Chronic Kidney Disease" OR "Kidney Insufficiency" OR "Kidney Dysfunction" OR "Renal Failure") AND ("Saliva" OR "Salivary Changes")
Scopus http://www.scopus.com/	("Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" OR "Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Dysfunction" OR "Kidney Dysfunction" OR "Renal Failure" OR "Renal Injury") AND ("Saliva" OR "Salivary Changes" OR "Salivary Flow" OR "Salivary pH" OR "Salivary Viscosity" OR "Salivary Phosphate" OR "Salivary Calcium" OR "Salivary Volume" OR "Salivary Composition")
Web of Science http://apps.webofknowledge.com/	("Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" OR "Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Dysfunction" OR "Kidney Dysfunction" OR "Renal Failure" OR "Renal Injury") AND ("Saliva" OR "Salivary Changes" OR "Salivary Flow" OR "Salivary pH" OR "Salivary Viscosity" OR "Salivary Phosphate" OR "Salivary Calcium" OR "Salivary Volume" OR "Salivary Composition")
Grey literature	
OpenGrey http://www.opengrey.eu/	("Kidney Diseases" OR Chronic Kidney Disease" OR "Kidney Insufficiency" OR "Kidney Dysfunction" OR "Renal Failure") AND ("Saliva" OR "Salivary Changes")
OpenThesis http://www.openthesis.org/	("Kidney Diseases" OR Chronic Kidney Disease" OR "Kidney Insufficiency" OR "Kidney Dysfunction" OR "Renal Failure") AND ("Saliva" OR "Salivary Changes")

the second phase, the abstracts of the studies were assessed with the initial application of the eligibility criteria. Titles that met the objectives of the study but did not have abstracts available were fully analyzed in the next phase. In the third phase, a full analysis of the texts of all eligible studies was carried out. Full texts published in languages other than English or Portuguese were translated to allow the application of the eligibility criteria. All phases were performed independently by two reviewers, and, in case of uncertainty or disagreement, a third reviewer (LRP) was consulted to make a final decision.

Data collection

Data collection from eligible articles was performed independently by two authors (RPCBR and MTCV). To ensure consistency of data extraction by the two authors, a third reviewer (WAV) conducted a calibration exercise with three eligible articles. In this calibration exercise, the authors were introduced to the information that should be collected from each eligible study and how it should be presented. At the end of the calibration exercise, the authors proceeded with data collection for the remainder of the eligible articles. Divergence in the information collected by the two authors was resolved by a third reviewer (WAV).

The following data were extracted from the articles: study identification (author, year, country, location, and application of ethical criteria), sample characteristics (number of CKD patients, number of healthy patients for studies requiring a control group, CKD stage of the patients, distribution by sex, and average age), collection and processing characteristics (method utilized for saliva collection, time of saliva collection, type of salivary analysis, and type of statistical analysis), and the main results (mean and standard deviation rate values of the flow rate, pH, and levels of phosphate and calcium of saliva, and main outcomes of each study). In cases where incomplete or insufficient information was present, the corresponding author was contacted via e-mail.

Risk of bias assessment

Two independent authors (RPCBR and WAV) assessed the risk of bias and individual quality of the eligible studies with the JBI Critical Appraisal Tools for use in the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies and the JBI Critical Appraisal Checklist for Analytical Quasi-experimental Studies, according to the respective study design [24]. For calibration, the authors analyzed an eligible study jointly in the presence of a third reviewer (LRP) responsible for solving the divergences in case of uncertainty.

Each study was categorized according to the percentage of positive answers to the questions corresponding to the assessment instrument. Each question could be answered as follows: “Yes”, if the study did not present biases for the domain assessed in the question; “No”, if the study presented biases for the domain assessed in the question; “Uncertain”, if the study did not provide sufficient information to assess the bias of the question; or “Not Applicable”, if the question did not fit in the study. The risk of bias was considered *High* when the study obtained 49% or less of “yes” answers, *Moderate* when the study obtained 50% to 69% of “yes” answers, and *Low* when the study reached 70% or more of “yes” answers [25].

Data synthesis and meta-analysis

The data collected were organized and described descriptively/narratively (qualitative synthesis) according to the findings presented in each study selected. Moreover, the quantitative data presented in each study were extracted, organized in tables, and then imported into the Stata 16.1 statistical software (StataCorp LLC, College Station, TX, USA). Only studies with specific data from patients in end-stage renal failure (stage 5) were included in the analysis.

To answer research question number 1, a meta-analysis was performed comparing the mean value of each indicator of interest (calcium concentration, salivary flow rate, phosphate concentration, phosphorus concentration, and salivary pH) between patients undergoing hemodialysis and healthy individuals. To answer research question number 2, the mean values of the same five indicators of interest, before and after hemodialysis, were compared. Although there were five indicators of interest, a meta-analysis was only considered if there were at least three studies for each indicator, otherwise, a combined measure was not estimated due to the limited number of studies.

In both questions, the calculated effect measure was the standardized mean difference. This measure represents the difference, in standard deviations, between the samples compared. On research question number 1, the effect measure was calculated directly with a meta-analysis for each indicator of interest. For research question number 2, considering that the samples compared were not independent of each other (repeated measures of the patients at two time points—before and after hemodialysis), a combined mean value was estimated for each indicator of interest at each time point. Finally, the standardized mean difference between the two groups was estimated, preventing biases in the effect measures calculated [26].

All meta-analyses were performed considering random effects, proposed by DerSimonian-Laird. Three heterogeneity measures were considered in the analyses: (1) I^2 statistics; (2) τ^2 statistics; (3) H^2 statistics. The I^2 represents the rate of variability among the studies caused by heterogeneity, excluding sample errors. The τ^2 represents the variance size among the studies, while H^2 represents the degree of heterogeneity among the studies, in which $H^2 = 1$ represents homogeneity. Meta-regressions were adjusted considering the method of saliva collection (stimulated or non-stimulated) and the average age of the participants of each study, to identify potential moderators. All analyses considered a 5% significance level.

Results

Study selection

During the first phase of the study selection, 4574 results were found distributed in nine electronic databases, including the "grey literature". After removing the duplicates, 3283 results remained for analysis. A careful analysis of the titles excluded 3078 results. Two hundred and five studies remained for abstract reviews. From those, 155 studies were excluded after applying the eligibility criteria. The 50 studies remaining were assessed. Seventeen studies were excluded and the reasons for exclusion were registered separately (Supplementary Table 1). Finally, thirty-three studies [6, 10, 13–16, 21, 27–52] were included in the qualitative analysis. Figure 1 presents the details of the process of search, identification, inclusion, and exclusion of studies.

Characteristics of eligible studies

Studies were published between 1999 and 2021 and conducted in 17 different countries, with 19 studies carried out in Asia, eight in Europe, three in South America, two in Africa, and one in Oceania. The total number of samples included 3147 participants, with 1969 CKD patients (cases) and 1178 healthy individuals (controls). The average age varied between 34.7 and 69.7 years among CKD patients and between 30.5 and 60.1 among healthy individuals. Men composed approximately 39% of the total sample among the studies that presented data related to participants' sex.

Five eligible studies [6, 21, 33, 36, 47] collected saliva of CKD patients at pre-dialysis and dialysis stages. Samples from all the other eligible studies presented patients with stage-5 CKD, which are patients who had undergone dialysis treatment, especially hemodialysis. Only three studies [32, 33, 43] reported patients who underwent peritoneal dialysis. For saliva collection, the eligible studies reported using non-stimulated and stimulated methods (with different stimulation practices). The time of saliva collection to which the patients were subjected varied between one and 15 min or the necessary time to reach a certain amount of saliva, which was previously established. Table 2 details the most relevant information of each eligible study and Table 3 presents the quantitative results and the main outcomes of the eligible studies in detail.

Risk of individual bias of the studies

In the risk of bias analysis of the cross-sectional eligible studies, 10 studies [6, 21, 31, 33, 36, 37, 39, 40, 45, 48] presented a low risk of bias, 15 studies [10, 15, 27–29, 32, 34, 35, 41, 42, 44, 46, 47, 49, 52] presented a moderate risk of bias, and one study [13] presented a high risk of bias or low methodological quality. In the analysis of the risk of bias of the quasi-experimental studies, all of them [14, 16, 30, 38, 43, 50, 51] presented a low risk of bias. Table 4 presents detailed information on the risk of bias of the eligible studies.

Synthesis of results and meta-analysis

The study by Thorman et al. [33] did not separate the quantitative data of patients undergoing hemodialysis or peritoneal dialysis, and the study by Savica et al. [31] did not present the quantitative data of the control group. Thus, only 31 studies were included in the meta- analyses.

CKD patients versus healthy individuals

A total of ten studies compared the mean values of calcium between the groups, showing high heterogeneity ($I^2 = 95.8\%$ and $H^2 = 23.7$). The mean values of salivary calcium concentration were similar when comparing CKD patients and healthy individuals (SMD = 0.39; 95% CI = − 0.37; 1.16; $p = 0.310$) (Fig. 2).

Regarding salivary flow rate, 17 studies were included in the analysis (Fig. 3). Similar to the concentrations of calcium, there was high heterogeneity among the studies ($I^2 = 94.3\%$ and $H^2 = 17.6$). Moreover, 90% of the studies included in this analysis had the same direction of effect, showing a reduced salivary flow rate in patients. The combined measure identified that salivary flow rate in CKD patients was 1.73 standard deviations (95% CI = − 2.14; − 1.31; $p < 0.001$) lower than healthy individuals.

The concentrations of phosphorus in the saliva of patients and healthy individuals were compared in four studies. There was no heterogeneity among the studies included ($I^2 = 0.0\%$ and $H^2 = 1.0$). The standardized mean difference was 0.86 standard deviations (95% CI = 0.63; 1.09; $p < 0.001$) higher in CKD patients than healthy individuals (Fig. 4).

Finally, the pH levels were also compared in 12 studies. The heterogeneity among studies was considered high ($I^2 = 91.9\%$ and $H^2 = 12.4$) but 78.5% of the studies included showed the same direction of effect (higher pH levels in patients). The combined measure estimated by the meta-analysis showed that the pH was 1.57 standard deviations

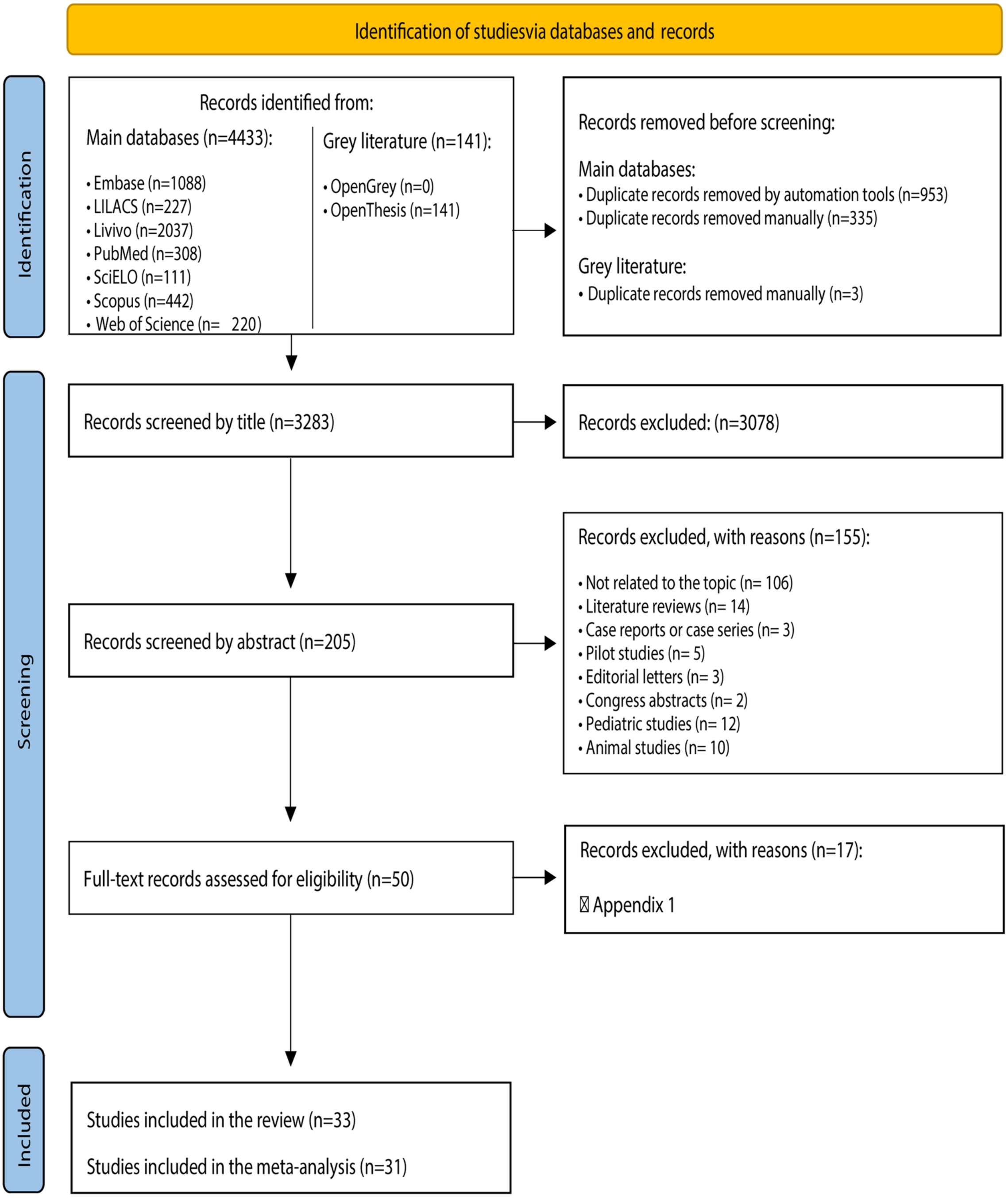

Fig. 1 Flowchart describing the search process and selection of eligible studies

(95% CI = 1.11; 2.03; $p < 0.001$) higher than healthy individuals (Fig. 5). The levels of phosphate were not compared because only two studies considered this indicator.

Before and after hemodialysis

The levels of calcium were similar before and after hemodialysis. It was not possible to compare the concentrations of phosphorus and phosphate in saliva. Conversely, the salivary flow rate was 0.53 standard deviations (95% CI = 0.25; 0.81) higher after hemodialysis, while the pH was 0.53 standard

Table 2 Summary of the main characteristics of the eligible studies

Authors, year (country of publication)[ref.]	Sample (n)	Sex (♀/♂)	Average age (years) ± SD (range)	CKD stage	Salivary parameters	Saliva collection method	Type of salivary analysis	Statistical analysis
Gavaldá et al. 1999 (Spain) [15]	Case: 105 Control: 53	Case: 52♀/53♂ Control: 24♀/29♂	Case: 58.9 ± 14.9 Control: 55.7 ± 10.7	5 (end stage)	Flow	Unstimulated, stimulated whole (citric acid) for 5 min; time of collection not reported	Flow: Volume divided by time	Student t-test, Chi-square test
Kho et al. 1999 (South Korea) [10]	Case: 22 Control: 22	Case: 8♀ / 14♂ Control: 8♀/14♂	Case: 34.7 ± 10.8 (18–59) Control: 30.5 ± 7.9	5 (end stage)	Flow and pH	Unstimulated for 10 min; collection occurred 1 day after hemodialysis, in the morning, before or 2 h after meals	Flow: Volume divided by time; pH: Electrometry	Student t-test
Bayraktar et al. 2002 (Turkey) [50]	Case: 50 Control: 48	Case: 27♀/23♂ Control: 23♀/25♂	Case: 46.7 ± 13.2 (21–69) Control: 45.7 ± 19.1 (16–86)	5 (end stage)	Flow	Stimulated (standard-weight paraffin wax) for 5 min; collection occurred in the morning, before hemodialysis	Flow: Volume divided by time	Student t-test
Postorino et al. 2002 (Italy) [51]	Case: 63 Control: 23	Case: 25♀/38♂ Control: 10♀/13♂	Case: 50.2 ± 13.8 (13–79) Control: 46.0 ± 13.2 (19–79)	5 (end stage)	Flow	Stimulated (chewing a gauze sponge) for 2 min and placed in a sterile plastic container	Flow: measured by gauze sponge weight and plastic container before and after chewing	Student t-test, Chi-square test
Bayraktar et al. 2004 (Turkey) [52]	Case: 72 Control: 50	Case: 34♀/38♂ Control: 26♀/24♂	Case: 45.05 ± 14.15 (18–68) Control: 43.92 ± 18.80 (18–86)	5 (end stage)	Flow and pH	Stimulated (standard-weight paraffin wax) for 5 min; collection occurred in the morning, before hemodialysis	Flow: Volume divided by time; pH: Merck indicator	Student t-test, Pearson's correlation, Chi-square Pearson's test
Martins et al. 2006 (Brazil)¶ [16]	Case: 15 Control: 15	Case: 5♀ / 10♂ Control: 11♀ / 4♂	Case: 47.4 ± 9.73 (32–64) Control: 39.8 ± 9.97 (22–55)	5 (end stage)	Flow, Calcium, and Phosphorus	Stimulated (chewing Parafilm) for 5 min; collection occurred immediately before and after hemodialysis	Flow: Volume divided by time; Calcium and Phosphorus: Spectrometry	ANOVA

Table 2 (continued)

Authors, year (country of publication)ref.	Sample (n)	Sex (♀/♂)	Average age (years) ± SD (range)	CKD stage	Salivary parameters	Saliva collection method	Type of salivary analysis	Statistical analysis
Bots et al. 2007 (Netherlands)¶ [30]	Case: 94	Case: 30♀/64♂	Case: 56.4 ± 16.7 (20–85)	5 (end stage)	Flow and pH	Unstimulated for 5 min and stimulated (chewing Parafilm) for 5 min; collection occurred immediately before, 1 h after, and 15 min after hemodialysis	Flow: Gravimetric; pH: Sentron electrolyte analyzer	MANOVA
Savica et al. 2007 (Italy) [28]	Case: 68 Control: 30	Case: 29♀/47♂ Control: 12♀/18♂	Case: 61.6 ± 9.4 Control: 52.3 ± 6.4	5 (end stage)	Calcium and Phosphorus	Unstimulated direct suction from the oral vestibule until collecting 2 mL; collection occurred before hemodialysis	Calcium and Phosphorus: Spectrometry	Kolmogorov–Smirnov test, Non-parametric Wilcoxon-Mann–Whitney rank sum test
Tomás et al. 2008 (Portugal) [6]	Case: 50 Control: 64	Case: 27♀/23♂ Control: 34♀ / 30♂	Case: 64 ± 11 Control: 60 ± 11	3, 4, and 5 (< 60 mL/min/1.73)	Flow, pH, and Calcium	Unstimulated (Salivette spitting method) for 5 min; collection occurred in the morning, before meals	Flow: Volume divided by time; pH and Calcium: Colorimetric and Selective Electrolyte Method	Student t-test; Mann–Whitney U-test, Kolmogorov–Smirnov test, Pearson's correlation
Bayraktar et al. 2009 (Turkey) [29]	Case: 176 (100 hemodialysis and 76 peritoneal dialysis) Control: 111	Case: 44♀ / 56♂ (hemodialysis) and 43♀ / 33♂ (peritoneal dialysis) Control: 65♀ / 46♂	Case: 46 ± 14 (hemodialysis) and 44 ± 12 (peritoneal dialysis) Control: 45 ± 18	5 (end stage)	Flow and pH	Stimulated (standard-weight paraffin wax) for 5 min; collection occurred in the morning, before hemodialysis	Flow: Volume divided by time; pH: Merck indicator	One-way ANOVA, Chi-square Pearson's test, Kruskal–Wallis test; Spearman rank test
Thorman et al. 2010 (Sweden) [30]	Case: 70 (40 predialysis, 21 hemodialysis, and 9 peritoneal dialysis) Control: 70	Case: § ♀/§ ♂ Control: § ♀ / § ♂	Case: § Control: §	4 and 5 (predialysis, hemodialysis, and peritoneal dialysis)	Flow	Unstimulated for 15 min and stimulated (paraffin wax) for 5 min; collection occurred in the morning	Flow: Volume divided by time	Student t-test

Table 2 (continued)

Authors, year (country of publication)[ref.]	Sample (n)	Sex (♀/♂)	Average age (years) ± SD (range)	CKD stage	Salivary parameters	Saliva collection method	Type of salivary analysis	Statistical analysis
Kaushik et al. 2013 (India) [31]	Case: 25 Control: 25	Case: § ♀ / § ♂ Control: § ♀ / § r♂	Case: § Control: §	5 (end stage)	Flow and pH	Unstimulated (spitting method) for 10 min and stimulated (paraffin wax) for 5 min; collection occurred in the morning, 1 day after hemodialysis	Flow: Volume divided by time; pH: Merck indicator	Student t-test
Babaee et al. 2014 (Iran) [32]	Case: 30 Control: 30	Case: 14♀/16♂ Control: 14♀ / 16♂	Case: 51.2 (35–65) Control: (30–65)	5 (end stage)	Flow	Unstimulated and stimulated (pilocarpine) for 5 min; collection occurred in the morning (between 8 and 12 a.m.)	Flow: measured by the weight of container in which saliva was collected	Mann–Whitney U-test, ANOVA
Belazelkovska et al. 2014 (Northern Macedonia) [33]	Case: 60 (30 predialysis and 30 hemodialysis) Control: 20	Case: 52♀ / 38♂ Control: § ♀ / §♂	Case: 46 ± 14 Control: §	4 and 5 (predialysis and hemodialysis)	Flow and pH	Unstimulated and stimulated (chewing gum) for 5 min; collection occurred in the morning or before hemodialysis	Flow: Gravimetric; pH: Electrolyte analyzer	Kruskal–Wallis-test, Mann–Whitney U-test, Spearman's rank test
Manley et al. 2014 (Australia) [34]	Case: 30 Control: 5	Case: 6♀ / 24♂ Control: 4♀ / 1♂	Case: 69.7 ± 14.2 Control: 44.6 ± 10.3	5 (end stage)	pH, Calcium, and Phosphate	Stimulated (chewing cotton swab from Salivette) until collecting 1 mL; collection occurred at least 2 h after meals	pH: §; Calcium and Phosphate: Indirect potentiometry, selective electrode enzymatic rate, and colorimetric methods	Wilcoxon rank-sum test
Seethalakshmi et al. 2014 (India)¶ [38]	Case: 30	Case: 14♀ / 16♂	Case: 50.33	5 (end stage)	Phosphate	Unstimulated, until collecting 5 mL; collection occurred before and after hemodialysis (without a specified time)	Phosphate: Automatic analyzer (colorimetric)	Student t-test

Table 2 (continued)

Authors, year (country of publication)[ref.]	Sample (n)	Sex (♀/♂)	Average age (years) ± SD (range)	CKD stage	Salivary parameters	Saliva collection method	Type of salivary analysis	Statistical analysis
Anuradha et al. 2015 (India) [13]	Case: 50 Control: 50	Case: § ♀/§ ♂ Control: § ♀ / § r♂	Case: § Control: §	5 (end stage)	Flow, Calcium, and Phosphorus	Unstimulated for 5 min; collection occurred in the morning, before hemodialysis	Flow: Volume divided by time; Calcium and phosphorus: End point colorimetry	Mann–Whitney U-test
Oyetola et al. 2015 (Nigeria) [36]	Case: 90 Control: 90	Case: § ♀/§ ♂ Control: § ♀ / § r♂	Case: § Control: §	5 (end stage)	Flow	Unstimulated (spitting method) for 5 min and stimulated (paraffin wax and lemon juice) for 5 min; collection occurred in the morning	Flow: Volume divided by time	Student t-test, Fisher's exact, Chi-square statistics
Rodrigues et al. 2016 (Brazil) [37]	Case: 60 Control: 37	Case: 31♀/29♂ Control: 23♀ / 14♂	Case: 45.6 ± 13.5 Control: 42.2 ± 14.3	5 (end stage)	Calcium and Phosphorus	Stimulated (paraffin wax) until collecting 5–10 mL; collection occurred during the first hour of hemodialysis session (case) and not reported for controls	Calcium and Phosphorus: Colorimetric	Chi-square test, Shapiro–Wilk test, Student t-test, Pearson's correlation
Hashemi et al. 2017 (Iran) [38]	Case: 44 Control: 44	Case: 23♀/21♂ Control: 23♀ / 21♂	Case: 46.98 ± 18.62 Control: 46.82 ± 18.55	5 (end stage)	Calcium and Phosphorus	Stimulated (Parafilm) until collecting 5 mL; collection occurred at least 1 h without eating or drinking	Calcium and Phosphorus: Colorimetric	Chi-square test, Student t-test, Pearson's correlation
Honarmand et al. 2017 (Iran) [39]	Case: 30 Control: 30	Case: § ♀/§ ♂ Control: § ♀ / § ♂	Case: 38.17 ± 16.88 Control: 40.30 ± 18.34	5 (end stage)	pH and Calcium	Unstimulated for 5 min; collection occurred in the morning (between 9 and 11 a.m.), before hemodialysis	pH: Electronic pH meter; Calcium: o-Cresolphthalein Method	Student t-test, Chi-square test

Table 2 (continued)

Authors, year (country of publication)[ref.]	Sample (n)	Sex (♀/♂)	Average age (years) ± SD (range)	CKD stage	Salivary parameters	Saliva collection method	Type of salivary analysis	Statistical analysis
Khanum et al. 2017 (India)¶ [14]	Case: 30	Case: §	Case: §	5 (end stage)	Flow, pH, and Calcium	Unstimulated for 5 min; collection occurred before and after hemodialysis, (without a specified time)	Flow: Volume divided by time; pH: Merck indicator; Calcium: Auto-analyzer	Chi-square test, Student t-test, Contingency coefficient analysis
Pham and Le 2019 (Vietnam) [21]	Case: 111 (27 in stage 3, 41 in stage 4, and 43 in stage 5) Control: 109	Case: 60♀/51♂ Control: 62♀ / 47♂	Case: 51.35 ± 12.93 Control: 48.24 ± 18.04	3a, 3b, 4, and 5	Flow and pH	Unstimulated and stimulated (paraffin wax) and duration of collection not reported; collection occurred in the morning	Flow: Volume divided by time; pH: Paper strips with electrolyte analyzer	Chi-square test, Mann-Whitney U-test
Alpdemir et al. 2018 (Turkey)¶ [43]	Case: 88 (44 hemodialysis and 44 peritoneal dialysis) Control: 40	Case: 14♀/30♂ (hemodialysis) and 18♀/26♂ (peritoneal dialysis) Control: 16♀ / 24♂	Case: 48.2 ± 12.3 (hemodialysis) and 45.8 ± 13.3 (peritoneal dialysis) Control: 43.9 ± 8.5	5 (end stage)	Calcium and Phosphate	Unstimulated for 5 min; collection occurred in the morning, before meals (controls and peritoneal dialysis); before and after hemodialysis	Calcium and Phosphate: Spectrophotometry	Kolmogorov–Smirnov test, Student t-test, Pearson's correlation
Eraly et al. 2018 (India) [44]	Case: 60 (20 with < 1 year, 20 between 1 and 3 years, and 20 > 3 years in hemodialysis) Control: 20	Case: § ♀/§ ♂ Control: § ♀ / § r♂	Case: § Control: §	5 (end stage)	Flow and pH	Stimulated (standard-weight paraffin wax) for 5 min; collection occurred in the morning (between 9 and 11 a.m.), after hemodialysis	Flow: Volume divided by time; pH: Test strip for 10 s	Kruskal–Wallis-test, Mann–Whitney U-test
Lasisi et al. 2018 (Nigeria) [45]	Case: 48 Control: 50	Case: 30♀/18♂ Control: 30♀ / 20♂	Case: 39.82 ± 11.07 Control: 39.1 ± 7.34	5 (end stage)	Calcium	Unstimulated (spitting method) until collecting 3 mL; collection occurred in the morning, before or 2 h after meals	Calcium: Indirect Colorimetric	Student t-test, Pearson's correlation

Table 2 (continued)

Authors, year (country of publication)ref.	Sample (n)	Sex (♀/♂)	Average age (years) ± SD (range)	CKD stage	Salivary parameters	Saliva collection method	Type of salivary analysis	Statistical analysis
Shetty et al. 2018 (India) [46]	Case: 60 (Group II: < 3 months; Group III: between 6 months and 2 years; and Group IV: > 2 years in hemodialysis) Control: 20	Case: § ♀/§ ♂ Control: § ♀ / § r♂	Case: § Control: §	5 (end stage)	Flow and pH	Stimulated (paraffin wax) for 5 min; collection occurred in the morning, after hemodialysis	Flow: Volume divided by time; pH: Saliva-check Kit	Kruskal–Wallis test, Mann -Whitney U-test
Marinoski et al. 2019 (Serbia) [47]	Case: 75 (50 predialysis and 25 hemodialysis) Control: 25	Case: 19♀/31♂ (predialysis) and 7♀/18♂ (hemodialysis) Control: 9♀/16♂	Case: 59.06 ± 14.30 (18–82) (predialysis) and 54.92 ± 13.60 (28–80) (hemodialysis) Control: 54.20 ± 12.67 (28–80)	4 and 5 (predialysis and hemodialysis)	Flow and pH	Unstimulated for 10 min; collection occurred in the morning (between 8 and 10 a.m.)	Flow: Volume divided by time; pH: Paper indicator	Kolmogorov–Smirnov test, ANOVA, Chi-square test, Howell test, Pearson's correlation
Tong et al. 2019 (China) [48]	Case: 30 Control: 35	Case: 15♀ / 15♂ Control: 20♀ / 15♂	Case: 49 ± 13 Control: 44 ± 11	5 (end stage)	pH	Unstimulated until collecting 1,5 mL; collection occurred in the morning, before meals	pH: Merck indicator	Student t-test, Wilcoxon rank sum test, Mann–Whitney U-test
Acosta et al. 2020 (Venezuela) [49]	Case: 12 Control: 12	Case: 6♀/6♂ Control: 5♀/7♂	Case: 48 Control: 30	5 (end stage)	Flow and Phosphate	Unstimulated for 1 min; collection time not reported	Flow and Phosphate: Colorimetric by Fiske & Subbarow	Student t-test
Zenuz et al. 2020 (Iran)¶ [50]	Case: 43	Case: 28♀/15♂	Case: 46 ± 19 (18–77)	5 (end stage)	Calcium and Phosphorus	Unstimulated for 5 min; collection occurred before and after hemodialysis, (without a specified time)	Calcium and Phosphorus: Automatic analyzer 902	Student t-test, Kolmogorov–Smirnov test, Wilcoxon test
Yu et al. 2021 (China)¶ [51]	Case: 100	Case: 66♀/34♂	Case: 62.45 ± 11.09 (34–85)	5 (end stage)	Flow, pH, and Calcium	Unstimulated for 5 min; collection occurred 1 h before and 1 h after hemodialysis	Flow: Volume divided by time; pH: Indicator strips; Calcium: Auto-analyzer	Descriptive statistics, Generalized Estimating Equations, Correlation matrix

Table 2 (continued)

Authors, year (country of publication)ref.	Sample (n)	Sex (♀/♂)	Average age (years) ± SD (range)	CKD stage	Salivary parameters	Saliva collection method	Type of salivary analysis	Statistical analysis
Teimoori et al. 2021 (Iran) [52]	Case: 48 Control: 48	Case: 20 ♀/28 ♂ Control: 20 ♀/28 ♂	Case: 53.48 ± 1.88 Control: 59.32 ± 1.63	5 (end stage)	Flow, pH, and Calcium	Unstimulated saliva samples collected with the spitting method before dialysis for 10 min; saliva samples were collected before meals or at least 2 h after meals	Flow: Volume divided by time; pH: Electronic pH meter	Descriptive statistics, Chi-square, t-test

¶—Quasi-experimental studies (Pre-Post Dialysis); §—Not reported by the study

deviations (95% CI = − 0.88; − 0.19) lower after hemodialysis (Table 5).

Discussion

This study investigated whether chronic kidney disease patients undergoing hemodialysis present changes in ionic composition, salivary flow rate, and salivary pH in comparison to healthy individuals. Additionally, it assessed the ability of one hemodialysis session to reverse these parameters. The meta-analyses showed that CKD patients had reduced salivary flow rate, increased salivary pH, and increased concentration of salivary phosphate, however, salivary flow rate alone was reversed after one hemodialysis session.

Maintaining an adequate salivary flow rate is important to prevent oral diseases such as caries and periodontitis, considering that low salivary flow rate is related to the maintenance of bacterial plaque and biofilm in the oral cavity [53–55]. The eligible studies that are present in this review and the results of the meta-analysis showed a significant reduction in the salivary flow rate of CKD patients. This finding can be related to oral manifestations often found in CKD patients, such as xerostomia, taste changes, and pale mucosa [13, 42, 47], although such association is not fully explained in the literature [30, 42, 47]. The reduction of salivary flow rate in CKD can be related to molecular changes in salivary glands due to medications used by CKD patients [29] or a reduction in the extracellular liquid volume of salivary glands, which relates to their hydration condition and hydroelectrolytic balance [6]. However, these phenomena are not well established.

Additionally, the results of the meta-analysis showed that one hemodialysis session can increase the salivary flow rate of CKD patients, reversing the changes established by CKD. One hypothesis for this finding is that the kidney ultrafiltration mechanism promoted by the hemodialysis procedure increases the intravascular volume leading to higher gland perfusion and consequently a higher production of saliva [51]. Considering that hemodialysis can reestablish the concentrations of sodium, potassium, bicarbonate, creatinine, and urea ions to values closer to the physiological level [56], it is suggested that the reestablishment of the hydroelectrolytic balance is related to the increase in salivary secretion after one hemodialysis session. It is known that increases in blood pressure are associated with increased sympathetic activity toward the salivary glands, which promotes increased glandular vasoconstriction and can reduce salivary flow rate [57]. Thus, the decrease in blood pressure, which is frequent in most hypertensive patients undergoing hemodialysis [58], can be related to the reestablishment of the sympathetic activity for salivary glands and salivary secretion after one hemodialysis session. This finding emphasizes

Table 3 Main results and outcomes of eligible studies investigating salivary parameters (salivary flow, pH, calcium, phosphate, and phosphorus levels)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Salivary flow (mL/min)						
Gavaldá et al. 1999 [15]	Case: U, 0.26 ± 0.28 S, 0.76 ± 0.38 Control: U, 0.28 ± 0.16 S, 1.26 ± 0.76	U, 8 S, 65	¥	¥	¥	The salivary flow of controls was significantly higher than sick individuals for the stimulated collection methods. There was no significant correlation between reduced flow in CKD patients and a greater formation of dental plaque and calculus
Kho et al. 1999 [10]	Case: U, 0.3 ± 0.18 Control: U, 0.45 ± 0.25	U, 50	¥	¥	¥	The salivary flow rate in CKD patients was significantly lower than controls
Bayraktar et al. 2002 [50]	Case: S, 0.8 ± 0.5 Control: S, 1.5 ± 0.5	S, 88	¥	¥	¥	The salivary flow in CKD patients was significantly lower than controls, regardless of the duration of dialytic therapy
Postorino et al. 2002 [51]	Case: ST, 1.65 ± 0.66 Control: ST, 2.05 ± 0.65	ST, 24	¥	¥	¥	The CKD patients presented lower salivary flow than controls and this reduction was mostly related to the degenerative changes in salivary glands
Bayraktar et al. 2004 [52]	Case: S, 0.69 ± 0.31 Control: S, 1.64 ± 0.44	S, 138	¥	¥	¥	The CKD patients presented significantly lower salivary flow rates than controls
Martins et al. 2006 ¶ [16]	Case: S, 0.81 ± 0.31 Control: S, 1.12 ± 0.2	S, 38	S, 0.81 ± 0.31	S, 1.18 ± 0.54	S, 46	The salivary flow rate of patients before the hemodialysis session was significantly lower than controls and patients after the hemodialysis session. These results help to validate the importance of hemodialysis in controlling salivary flow and composition

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Bots et al. 2007 ¶ [30]	¥	¥	U, 0.3 ± 0.23 S, 1.05 ± 0.71	U, 0.41 ± 0.25 S, 1.23 ± 0.74	U, 37 S, 17	In both saliva collection methods (non-stimulated and stimulated), the salivary flow rate in the patients analyzed was significantly higher after the hemodialysis session than the flow rate before the session
Tomás et al. 2008 [6]	Case: U, 0.39 ± 0.13 Control: U, 0.35 ± 0.14	U, -10	¥	¥	¥	The salivary flow rate did not show significant changes between CKD patients at moderate, severe, and end stages and controls. The relationship between the salivary changes detected and oral health status has not been completely established
Bayraktar et al. 2009 [29]	Case: S, 0.7 ± 0.32 Control: S, 1.64 ± 0.45	S, 134	¥	¥	¥	The salivary flow in healthy patients was significantly higher than CKD patients undergoing hemodialysis. Decreased salivary flow rates were related to an increased risk of caries
Thorman et al. 2010 [30]	Case with HD and PD: U, 0.2 ± 0.22 S, 1.3 ± 0.73 Control: U, 0.3 ± 0.19 S, 1.9 ± 1.25	U, 50 S, 46	¥	¥	¥	The stimulated salivary flow rate presented a significant reduction among sick individuals, regardless of CKD stage, when compared to controls. The non-stimulated flow rate did not show significant changes between the groups of CKD patients and controls
Babaee et al. 2014 [32]	Case: U, 0.31 ± § S, 0.47 ± § Control: U, 0.48 ± § S, 0.75 ± §	U, 55 S, 60	¥	¥	¥	Salivary flow was significantly lower in CKD patients than controls for both saliva collection methods. This can be related to the xerostomia reported by sick individuals

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Belazelkovska et al. 2014 [33]	Case: U, 0.31 ± 0.21 S, 0.59 ± 0.35 Control: U, 0.54 ± 0.2 S, 1.9 ± 0.42	U, 74 S, 222	¥	¥	¥	Patients undergoing hemodialysis presented lower significant salivary flow rates than controls. The flow reduction affected the oral conditions of patients negatively, with the occurrence of oral manifestations and lesions
Anuradha et al. 2015 [13]	Case: U, 0.41 ± § Control: U, 0.48 ± §	U, 17	¥	¥	¥	Salivary flow was significantly lower in CKD patients than controls. The most common oral manifestations in CKD patients were pale mucosa, dental hypoplasia, metallic taste, and fissured tongue
Oyetola et al. 2015 [36]	Case: U, 0.47 ± 0.2 S, 0.81 ± 0.38 Control: U, 0.76 ± 0.45 S, 1.61 ± 0.79	U, 62 S, 99	¥	¥	¥	The CKD patients presented significantly lower stimulated and non-stimulated salivary flow rates than controls. The decreased flow showed a significant relationship with oral effects such as taste changes, burning sensation, and halitosis
Kaushik et al. 2016 [31]	Case: U, 0.31 ± 0.01 S, 0.66 ± 0.02 Control: U, 0.52 ± 0.06 S, 1.16 ± 0.11	U, 68 S, 76	¥	¥	¥	The patients presented significantly lower salivary flow rates than controls for both saliva collection methods. Oral manifestations such as bad odor and xerostomia were verified in patients and can be related to the reduced salivary flow
Khanum et al. 2017 [14] ¶	¥	¥	U, 0.46 ± 0.27	U, 0.84 ± 0.24	U, 83	The salivary flow rate of patients increased significantly after the hemodialysis session. The salivary changes affected the oral clinical findings
Pham and Le 2019 [21]	Case: U, 0.11 ± 0.02 Control: U, 0.38 ± 0.11	U, 245	¥	¥	¥	The non-stimulated salivary flow rate was significantly lower in CKD patients than controls

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Eraly et al. 2018 [44]	Case with DD < 1 year: S, 1.2 ± 0.61 Case with HD between 1 and 3 years: S, 0.98 ± 0.5 Case with HD > 3 years: S, 0.89 ± 0.45 Control: S, 1.47 ± 0.52	Case with HD < 1 year X Control: 23 Case with HD between 1 and 3 years X Control: 50 Case with HD > 3 years X Control: 65	¥	¥	¥	The salivary flow of CKD patients decreased as the dialytic treatment time increased, and the times of dialysis between 1 and 3 years and more than 3 years presented a significant difference compared to the control group
Shetty et al. 2018 [46]	Case with HD < 3 months: S, 1.31 ± 0.34 Case with HD between 6 months and 2 years: S, 0.99 ± 0.32 Case with HD > 2 years: S, 0.73 ± 0.26 Control: S, 1.84 ± 0.34	Case with HD < 3 months X Control: 40 Case with HD between 6 months and 2 years X Control: 86 Case with HD > 2 years X Control: 152	¥	¥	¥	All groups of patients undergoing hemodialysis presented significantly lower salivary flow rates than controls, and the lowest flow occurred in the groups undergoing hemodialysis with the longest dialysis vintage
Marinoski et al. 2019 [47]	Case: U, 0.3 ± 0.16 Control: U, 0.51 ± 0.19	U, 70	¥	¥	¥	The salivary flow rate of sick individuals, regardless of group, was significantly lower than the salivary flow rate of controls
Acosta et al. 2020 [49]	Case: U, 0.69 ± § Control: U, 0.88 ± §	U, 28	¥	¥	¥	The CKD patients presented a reduced salivary flow compared to controls
Yu et al. 2021 [51] ¶	¥	¥	U, 0.15 ± 0.1	U, 0.19 ± 0.12	U, 27	The salivary flow rate increased significantly after the hemodialysis session
Teimoori et al. 2021 [52]	Case: U, 0.23 ± 0.08 Control: U, 0.34 ± 0.13	U, 48	¥	¥	¥	The CKD patients presented a reduced salivary flow compared to controls

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Salivary pH						
Kho et al. 1999 [10]	Case: U, 7.51 ± 0.44 Control: U, 6.62 ± 0.22	U, − 12	¥	¥	¥	The pH was significantly higher in sick individuals. The patients presented oral changes such as uremic odor, dry mouth, and taste changes that can be related to salivary changes
Bayraktar et al. 2004 [52]	Case: S, 8.15 ± 0.72 Control: S, 7.16 ± 0.75	S, − 12	¥	¥	¥	The CKD patients presented significantly higher pH levels than controls. There was no relationship between the changes in salivary flow and pH and the negative results of the DMFT index in patients
Bots et al. 2007 [30] ¶	¥	¥	U, 7.2 ± 0.6 S, 7.3 ± 0.5	U, 6.7 ± 0.5 S, 6.9 ± 0.9	U, − 7 S, − 5	The pH of patients significantly reduced after the hemodialysis session. These results help to affirm that hemodialysis produces acute effects in the saliva of patients undergoing treatment
Tomás et al. 2008 [6]	Case: U, 7.71 ± 1.18 Control: U, 6.79 ± 0.77	U, − 12	¥	¥	¥	The pH was significantly high in CKD patients when compared to controls. The relationship between the salivary changes detected and oral health status has not been completely established
Bayraktar et al. 2009 [29]	Case: S, 8.12 ± 0.32 Control: S, 7.16 ± 0.76	S, − 12	¥	¥	¥	The pH was significantly higher in CKD patients than controls
Kaushik et al. 2013 [31]	Case: U, 7.24 ± 0.25 S, 7.28 ± 0.25 Control: U, 6.6 ± 0.32 S, 7.24 ± 0.25	U, − 9 S, − 1	¥	¥	¥	The pH of patients was significantly higher than controls only in the non-stimulated collection method
Belazelkovska et al. 2014 [33]	Case: U, 7.26 ± 0.35 S, 6.91 ± 0.35 Control: U, 7.34 ± 0.05 S, 6.78 ± 0.32	U, 1 S, − 2	¥	¥	¥	The changes in pH were not significant for both saliva collection methods between CKD patients and controls
Manley 2014 [34]	Case: S, 6.98 ± 0.24 Control: S, 6.72 ± 0.21	S, − 4	¥	¥	¥	The pH did not show significant changes between CKD patients and controls

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Honarmand et al. 2017 [39]	Case: U, 8.41 ± 0.76 Control: U, 7.01 ± 0.31	U, − 17	¥	¥	¥	The salivary pH of CKD patients was significantly higher than the salivary pH of the control group
Khanum et al. 2017 [14] ¶	¥	¥	U, 6.39 ± 1.1	U, 6.54 ± 0.6	U, 2	The pH did not show significant changes in the analyses before and after hemodialysis. The salivary changes affected the oral clinical findings
Pham and Le 2019 [21]	Case: U, 7.8 ± § Control: 7.0 ± §	U, − 10	¥	¥	¥	The salivary pH of CKD patients was significantly higher than the control group
Eraly et al. 2018 [44]	Case with HD < 1 year: S, 6.84 ± 0.45 Case with HD between 1—3 years: S, 6.99 ± 0.42 Case with HD > 3 years: S, 7.21 ± 0.26 Control: S, 6.65 ± 0.27	Case with HD < 1 year X Control: − 3 Case with HD between 1 and 3 years X Control: − 5 Case with HD > 3 years X Control: − 8	¥	¥	¥	The salivary pH of CKD patients increased as the dialytic treatment time increased, and all groups of CKD patients presented significant differences when compared to the control group
Shetty et al. 2018 [46]	Case with HD < 3 months: S, 6.38 ± 0.32 Case with HD between 6 months and 2 years: S, 6.75 ± 0.35 Case with HD > 2 years: S, 7.33 ± 0.35 Control: S, 6.02 ± 0.27	Case with HD < 3 months X Control: − 6 Case with HD between 6 months and 2 years X Control: − 11 Case with HD > 2 years X Control: − 18	¥	¥	¥	The pH was significantly higher among sick individuals, increasing according to longer times of hemodialysis
Marinoski et al. 2019 [47]	Case: U, 6.88 ± 0.22 Control: U, 6.52 ± 0.49	U, -5	¥	¥	¥	The salivary pH of CKD patients was significantly higher than controls
Tong et al. 2019 [48]	Case: U, 8.2 ± 0.44 Control: U, 7.5 ± 0.37	U, − 9	¥	¥	¥	The CKD patients presented a significantly higher pH than controls
Yu et al. 2021 [51] ¶	¥	¥	U, 7.83 ± 0.75	U, 7.3 ± 0.83	U, − 7	The pH of patients was significantly reduced after the hemodialysis session
Teimoori et al. 2021 [52]	Case: U, 7.74 ± 0.29 Control: U, 6.61 ± 0.20	U, − 15	¥	¥	¥	The CKD patients presented a significantly higher pH than controls

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Salivary calcium levels (mg/dL)						
Martins et al. 2006 [16] ¶	Case: S, 1.72 ± 0.7 Control: S, 1.42 ± 0.62	S, − 17	S, 1.72 ± 0.7	S, 1.5 ± 0.48	S, − 13	The calcium levels did not show significant changes between the groups
Savica et al. 2007	Case: U, 7.21 ± § Control: §	¥	¥	¥	¥	The data on salivary calcium levels of the control group were not presented
Tomás et al. 2008 [6]	Case: U, 2.64 ± 2.84 Control: U, 7.12 ± 5.92	U, 170	¥	¥	¥	The salivary calcium levels were significantly lower in CKD patients than controls. The relationship between the salivary changes detected and oral health status has not been completely established
Manley 2014 [34]	Case: S, 12.12 ± 1.72 Control: S, 12.92 ± 0.28	S, 7	¥	¥	¥	The calcium levels did not present significant changes between CKD patients and controls. However, the salivary calcium levels presented a significant relationship with the symptoms of dry mouth reported by sick individuals
Anuradha et al. 2015 [13]	Case: U, 4.31 ± 4.65 Control: U, 6.5 ± 2.3	U, 51	¥	¥	¥	The calcium levels were significantly higher in controls than sick individuals
Rodrigues et al. 2016 [37]	Case: S, 5.36 ± 2.31 Control: S, 1.87 ± 1.37	S, − 65	¥	¥	¥	The salivary calcium levels in CKD patients were significantly higher than the levels of controls
Hashemi et al. 2017 [38]	Case: S, 6.42 ± 1.99 Control: S, 2.92 ± 1.28	S, − 55	¥	¥	¥	The salivary calcium levels were significantly higher in CKD patients than controls, therefore, they can represent potential non-invasive diagnostic biomarkers
Honarmand et al. 2017 [39]	Case: U, 2.23 ± 1.15 Control: U, 2.47 ± 1.33	U, 11	¥	¥	¥	The salivary calcium levels in CKD patients were lower than the control group but this difference was not significant

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Khanum et al. 2017 [14] ¶	¥	¥	U, 8.77 ± 0.53	U, 8.76 ± 0.52	U, 0	The salivary calcium levels did not show significant changes in the analyses before and after hemodialysis
Alpdemir et al. 2018 [43] ¶	Case: U, 1.52 ± 1.68 Control: U, 3.32 ± 2.2	U, 118	U, 1.52 ± 1.68	U, 2.93 ± 2.36	U, 93	The salivary calcium levels were significantly lower in CKD patients than controls but the values had a tendency to increase after the hemodialysis session
Lasisi et al. 2018 [45]	Case: U, 6.82 ± 3.23 Control: U, 1.68 ± 1.09	U, -71	¥	¥	¥	The calcium levels in CKD patients were significantly higher than controls. High calcium levels in CKD patients suggest its role in the low prevalence of caries in CKD patients
Zenuz et al. 2020 [50] ¶	¥	¥	U, 6.35 ± 5.29	U, 5.68 ± 2.49	U, − 11	The salivary calcium levels in CKD patients decreased after the hemodialysis session but the reduction values were not statistically significant
Yu et al. 2021 [51] ¶	¥	¥	U, 8.32 ± 6.92	U, 11.0 ± 8.04	U, 155	The calcium levels were significantly higher after the hemodialysis session
Teimoori et al. 2021 [52]	Case: U, 3.17 ± 3.22 Control: U, 1.77 ± 1.41	U, -44	¥	¥	¥	The calcium levels in CKD patients were significantly higher than controls
Salivary phosphate levels (mg/dL)						
Manley 2014 [34]	Case: S, 30.74 ± 3.75 Control: S, 21.16 ± 4.83	S, − 31	¥	¥	¥	The phosphate levels did not present significant changes between CKD patients and controls. However, the salivary phosphate levels presented a significant relationship with the symptoms of dry mouth reported by sick individuals

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Seethalakshmi et al. 2014 [38] ¶	¥	¥	U, 21.1 ± 7.99	U, 19.09 ± 7.61	U, − 10	The salivary phosphate levels in CKD patients were higher before the hemodialysis session than the levels after the hemodialysis session
Alpdemir et al. 2018 [43] ¶	Case: U, 5.51 ± 1.64 Control: U, 3.65 ± 0.62	U, − 34	U, 5.51 ± 1.64	U, 2.66 ± 0.9	U, − 52	The salivary phosphate levels were significantly higher in CKD patients before the hemodialysis session and had a tendency to normalize after the treatment
Acosta et al. 2020 [49]	Case: U, 3.19 ± § Control: U, 2.57 ± §	U, − 19	¥	¥	¥	The phosphate levels were high in CKD patients due to the retention of the ion in the organism by the disease, but the values were not significant. This can be related to higher indices of dental calculus
Salivary phosphorus levels (mg/dL)						
Martins et al. 2006 [16] ¶	Case: S, 3.04 ± 1.57 Control: S, 1.83 ± 0.64	S, − 40	S, 3.04 ± 1.57	S, 1.83 ± 0.64	S, − 40	The salivary phosphorus levels in CKD patients before hemodialysis were significantly higher than controls and CKD patients after hemodialysis. These results help to validate the importance of hemodialysis in controlling salivary flow and composition
Savica et al. 2007	Case: U, 30.27 ± § Control: U, 12.1 ± §	U, − 60	¥	¥	¥	The salivary phosphorus levels in CKD patients were significantly higher than controls
Anuradha et al. 2015 [13]	Case: U, 9.26 ± 4.25 Control: U, 5.6 ± 3.7	U, − 40	¥	¥	¥	The phosphorus levels were significantly higher in CKD patients than the levels in the control group

Table 3 (continued)

Authors, year	Mean ± SD	Mean difference (%)	Pre-dialysis mean ± SD	Post-dialysis mean ± SD	Mean difference (%)	Main outcomes
Rodrigues et al. 2016 [37]	Case: S, 18.36 ± 7.58 Control: S, 13.96 ± 4.21	S, − 24	¥	¥	¥	The salivary phosphorus levels in CKD patients were significantly higher than the levels of controls. Secondary conditions such as hypothyroidism seem to be associated with the high concentrations of salivary phosphorus
Hashemi et al. 2017 [38]	Case: S, 5.55 ± 1.38 Control: S, 4.49 ± 0.68	S, -19	¥	¥	¥	The salivary phosphorus levels were significantly higher in CKD patients than controls, therefore, they may represent potential non-invasive diagnostic biomarkers
Zenuz et al. 2020 [50] ¶	¥	¥	U, 31.1 ± 17.8	U, 27.7 ± 16.3	U, − 11	The salivary phosphorus levels in CKD patients decreased after the hemodialysis session but the reduction values were not statistically significant

¶—Quasi-experimental studies (before and after hemodialysis); ¥—Not applicable to the study; §—Not reported; U—Non-stimulated saliva; S—Stimulated saliva

Table 4 Risk of bias assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies (Moola et al. 2020) and the JBI Critical Appraisal Checklist for Analytical Quasi-experimental Studies (Tufanaru et al. 2020)

Author, year	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	% yes/ risk
Cross-sectional studies										
Gavaldá et al. 1999 [15]	–	√	U	√	–	–	√	√	*	50/ Moderate
Kho et al. 1999 [10]	√	√	–	√	–	–	√	√	*	62.5/ Moderate
Bayraktar et al. 2002 [50]	–	√	–	√	–	–	√	√	*	50/ Moderate
Postorino et al. 2002 [51]	√	√	–	√	–	–	√	√	*	62.5/ Moderate
Bayraktar et al. 2004 [52]	–	√	–	√	–	–	√	√	*	50/ Moderate
Savica et al. 2007	√	√	–	√	√	√	√	√	*	87.5/ Low
Tomás et al. 2008 [6]	√	√	√	√	√	√	√	√	*	100/ Low
Bayraktar et al. 2009 [29]	√	√	–	√	–	–	√	√	*	62.5/ Moderate
Thorman et al. 2010 [30]	√	√	√	√	–	–	√	√	*	75/ Low
Babaee et al. 2014 [32]	–	√	–	√	–	–	√	√	*	50/ Moderate
Belazelkovska et al. 2014 [33]	√	√	√	√	–	–	√	√	*	75/ Low
Manley 2014 [34]	√	√	√	√	–	–	√	√	*	75/ Low
Anuradha et al. 2015 [13]	–	U	U	√	–	–	√	√	*	37.5/ High
Oyetola et al. 2015 [36]	√	√	U	√	√	√	√	√	*	87.5/ Low
Rodrigues et al. 2016 [37]	√	√	√	√	–	–	√	√	*	75/ Low
Kaushik et al. 2016 [31]	√	√	–	√	–	–	√	√	*	62.5/ Moderate
Hashemi et al. 2017 [38]	√	√	–	√	–	–	√	√	*	62.5/ Moderate
Honarmand et al. 2017 [39]	√	√	–	√	–	–	√	√	*	62.5/ Moderate
Pham and Le 2019 [21]	√	√	√	√	√	√	√	√	*	100/ Low
Eraly et al. 2018 [44]	√	U	–	√	–	–	√	√	*	50/ Moderate
Lasisi et al. 2018 [45]	√	√	√	√	–	–	√	√	*	75/Low
Shetty et al. 2018 [46]	√	U	–	√	–	–	√	√	*	50/ Moderate
Marinoski et al. 2019 [47]	√	√	U	√	–	–	√	√	*	62.5/ Moderate
Tong et al. 2019 [48]	√	√	√	√	–	–	√	√	*	75/ Low
Acosta et al. 2020 [49]	√	√	–	√	–	–	√	√	*	62.5/ Moderate
Teimoori et al. 2021 [52]	√	–	U	√	–	–	√	√	*	50/ Moderate
Quasi-experimental studies										
Martins et al. 2006 [16]	√	√	√	√	U	NA	√	√	√	87.5/ Low
Bots et al. 2007 [30]	√	√	√	–	U	NA	√	√	√	75/ Low
Seethalakshmi et al. 2014 [38]	√	√	√	–	U	NA	√	√	√	75/ Low
Khanum et al. 2017 [14]	√	√	√	–	U	NA	√	√	√	75/ Low
Alpdemir et al. 2018 [43]	√	√	√	√	U	NA	√	√	√	87.5/ Low
Zenuz et al. 2020 [50]	√	√	√	–	U	NA	√	√	√	75/ Low
Yu et al. 2021 [51]	√	√	√	–	U	NA	√	√	√	75/ Low

√—yes; —No; U- Unclear; NA—Not applicable; *—Not related to the study

the importance of hemodialysis not only for filtering toxic molecules but also for improving oral health [14, 51].

The salivary pH was another major aspect investigated in several eligible studies. The results of the meta-analysis showed that salivary pH is higher in CKD patients when compared to healthy individuals. This may be justified by the fact that CKD patients present high levels of urea in their salivary composition [43], which is metabolized by the oral microflora into carbon dioxide and ammonia [59], thus increasing the salivary pH [42]. In this context, considering that an acidic pH favors the demineralization process of the dental structure [60], it can be correlated to a lower prevalence of caries in CKD patients, even though salivary flow rate is also often reduced [61]. Considering that a low salivary pH provides an acidogenic environment for the growth of aciduric bacteria that in turn leads to dental caries [60], a higher pH can work as a protective factor for enamel demineralization.

Although hemodialysis can reduce the concentration of urea in saliva [25], the results of the present meta-analysis showed that this isolated factor was not sufficient to reduce the salivary pH immediately after hemodialysis. This result can be justified by the fact that the studies collected saliva immediately after the dialysis procedures, which can represent a short time to assess the changes in the metabolism of urea in intracellular mechanisms of acinar cells from the

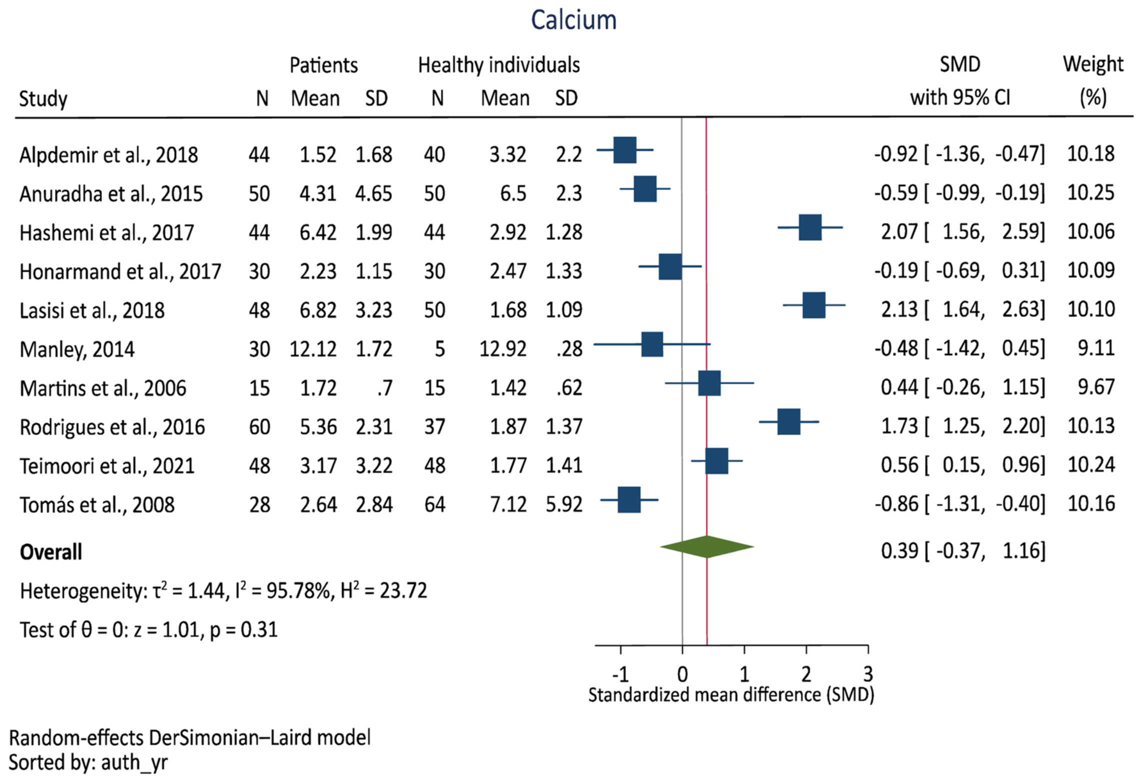

Fig. 2 Meta-analysis of calcium concentration levels between patients undergoing hemodialysis and healthy individuals

salivary gland, and consequently a reduction in salivary pH. Further studies should be performed to observe the influence of hemodialysis in salivary pH for longer intervals after the hemodialysis session.

The level of salivary calcium is also another important biomarker in CKD patients. It is believed that higher concentrations of calcium in saliva can not only work as a protective factor for the development of caries but also as a risk factor for the formation of calculus [62, 63]. Although some eligible studies in this review highlighted the association of CKD patients with higher chances of presenting dental calculus [15, 34, 42, 49], there is no consistent evidence confirming this association and it was not the objective of the present review. Moreover, the results of this meta-analysis did not show significant changes in the levels of calcium in CKD patients when compared to healthy patients, despite the high inconsistency found in the individual results of the studies. We believe there is no standardized methodology in the studies, which used different laboratory methods to calculate the levels of calcium in saliva, besides the population differences. This prevents drawing more categorical conclusions about such a variable.

The levels of salivary phosphorus and phosphate just like calcium are important biomarkers that can be affected by CKD and are described as potential ways of assessing the need for hemodialysis [40]. The present meta-analysis evidenced increased levels of salivary phosphorus in CKD patients in comparison to healthy individuals, which can be justified by the pathophysiological changes in the kidneys that increase this component in plasma and saliva.

We emphasize that the results of these meta-analyses should be interpreted with caution due to the high heterogeneity of analyses that could not be explained by meta-regression analyses, which can be justified by the different populations and methodologies used to assess this variable and the clinical characteristics of patients that could not be assessed individually, such as comorbidities associated with CKD, dialysis vintage, age group, and medication use. However, to the best of our knowledge, this systematic review of the literature is the first to investigate the salivary changes of CKD patients and assess the effects of hemodialysis in saliva. Moreover, an extensive literature search without restrictions of publication year or language ensured the inclusion of a maximum number of published studies.

From the dental clinic standpoint, this systematic review draws attention to major salivary changes that should be considered when planning dental treatment for patients with kidney failure, such as xerostomia, taste changes caused by reduced salivary flow rate, monitoring of the periodontal condition, and the appearance of oral lesions, in an effort to reduce the impact of these oral manifestations on the quality of life of those patients.

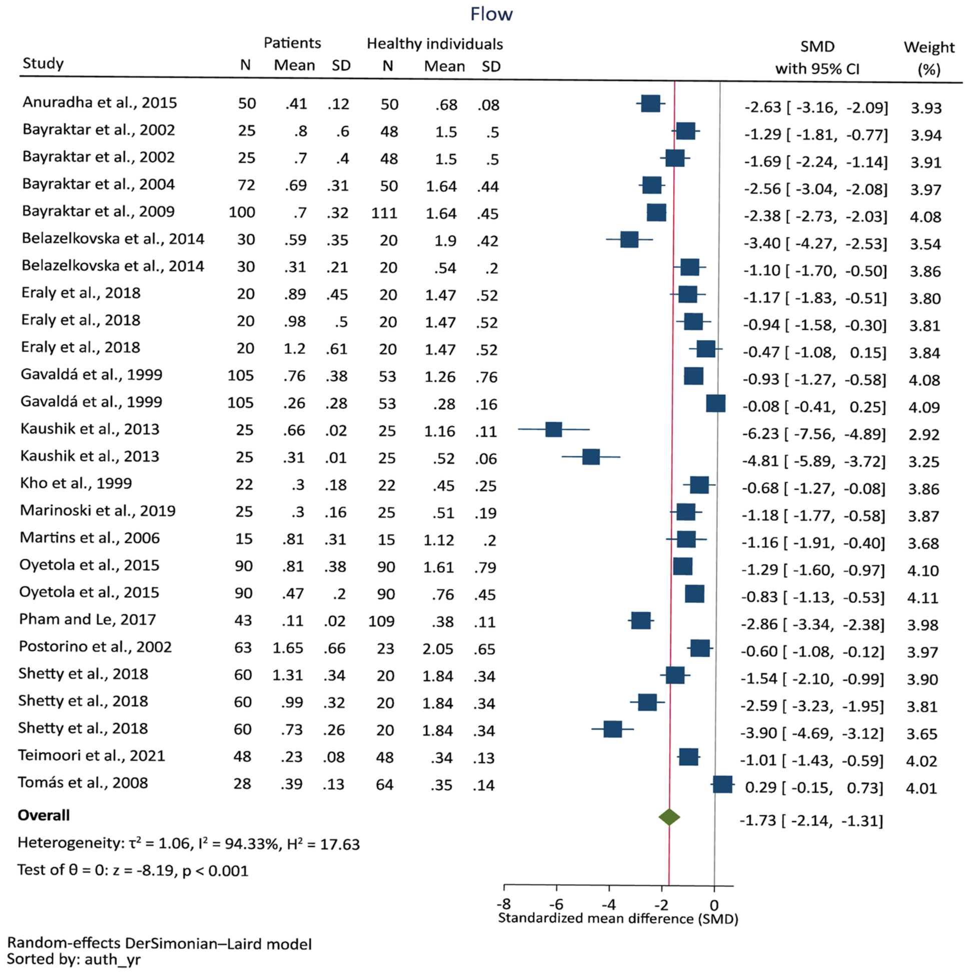

Fig. 3 Meta-analysis of salivary flow rate between patients undergoing hemodialysis and healthy individuals

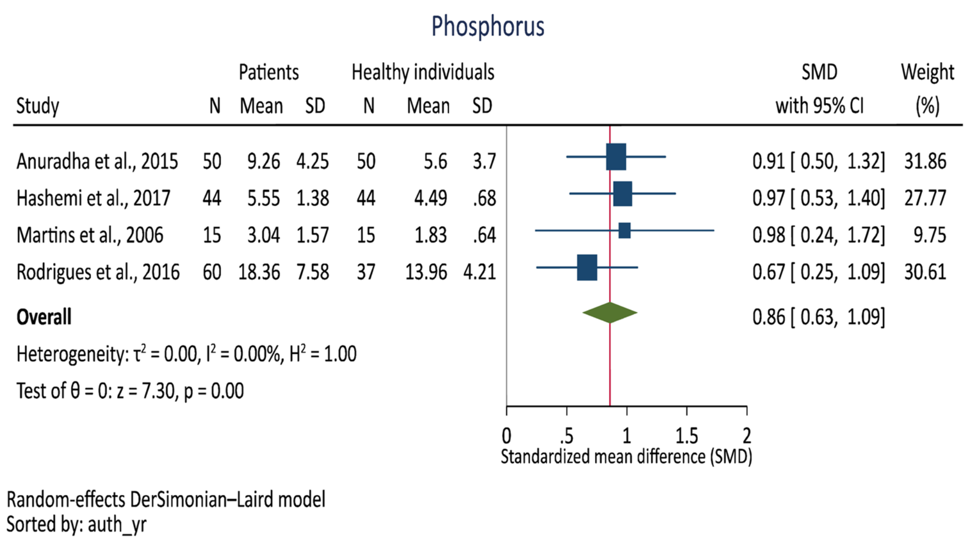

Fig. 4 Meta-analysis of phosphorus concentration levels between patients undergoing hemodialysis and healthy individuals

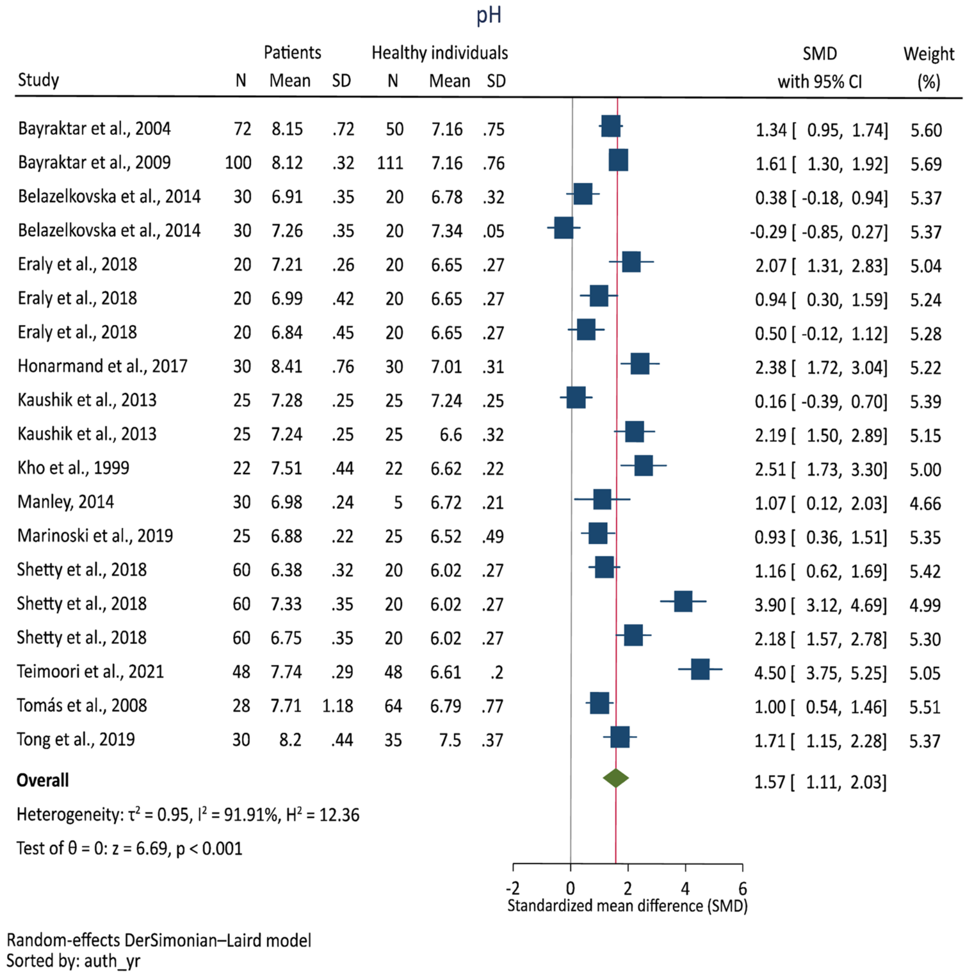

Fig. 5 Meta-analysis of pH concentration levels between patients undergoing hemodialysis and healthy individuals

Table 5 Combined means and standardized mean differences after the meta-analysis of the concentration levels of calcium, pH, and salivary flow at two time points: before and after hemodialysis

Indicator	Combined mean before hemodialysis (95% CI)	Combined mean after hemodialysis (95% CI)	Combined standardized mean difference (95% CI)
$Calcium_5$	4.54 (0.69; 8.38)	5.97 (1.07; 10.9)	0.24 (– 0.26; 0.75)
$Flow_5$	0.55 (0.09; 1.01)	0.77 (0.18; 1.34)	0.53 (0.25; 0.81)
$Phosphate_2$	–[a]	–[a]	–[a]
$Phosphorus_2$	–[a]	–[a]	–[a]
pH_4	7.18 (6.23; 8.13)	6.86 (6.34; 7.38)	– 0.53 (– 0.88; – 0.19)

[a]Insufficient number of studies to estimate combined measures (two studies or less). Subscribed numbers indicate the number of studies considered in each analysis

Conclusion

Chronic kidney disease patients present major changes in salivary properties and composition, such as reduced flow rate and increased salivary pH, as well as higher levels of phosphorus, but with no differences in calcium and phosphate levels when compared to healthy individuals. It was also verified that hemodialysis can increase the salivary flow rate of these patients. These findings can assist in the understanding of the oral manifestations of chronic kidney disease patients and raise awareness of the need for customized clinical planning of dental care in this group of patients.

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Declarations

Conflict of interest None.

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