



**Universidade Federal de Uberlândia**  
**Faculdade de Odontologia**  
**Programa de Pós-Graduação em Odontologia**



Renata Prata Cunha Bernardes Rodrigues

**Alterações salivares em pacientes adultos diagnosticados com doença renal crônica**

*Salivary changes in adult patients diagnosed with chronic kidney disease*

Tese apresentada à Faculdade de Odontologia da Universidade Federal de Uberlândia, como requisito parcial para obtenção do Título de Doutora em Odontologia na Área de Concentração de Clínica Odontológica Integrada.

Uberlândia

2021

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Uberlândia

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**UNIVERSIDADE FEDERAL DE UBERLÂNDIA**  
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## **DEDICATÓRIA**

À Deus, pela vida e pelas bênçãos recebidas.

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## RESUMO

A doença renal crônica é um importante problema de saúde, com prevalência estimada em torno de 11% da população adulta mundial. Pacientes com essa doença, podem apresentar alterações na composição salivar, já que esse fluido está diretamente relacionado à composição sanguínea. O objetivo foi de avaliar as evidências existentes quanto à relação entre o diagnóstico de doença renal crônica e alterações salivares em pacientes adultos. No *Capítulo 1* - busca em oito bases de dados para verificar o uso de creatinina e ureia salivar no diagnóstico de doença renal crônica. Apenas estudos de teste diagnóstico foram incluídos. A ferramenta JBI foi utilizada para avaliar o risco de viés. Uma meta-análise de proporções foi realizada e a ferramenta GRADE foi utilizada para avaliar a certeza de evidência das estimativas. *Capítulo 2* - Oito bases de dados utilizadas para identificar estudos antes e depois com pacientes com doença em hemodiálise. A ferramenta JBI foi usada para o risco de viés. Metanálises foram conduzidas para comparar a correlação salivar e sérica e para agrupar as diferenças de proporção e média de pré e pós-hemodiálise dos níveis de ureia e creatinina. A abordagem GRADE foi usada para avaliar a certeza da evidência. *Capítulo 3* - busca em nove bases de dados a fim de localizar estudos clínicos observacionais, sem restrição de ano ou idioma de publicação. Dois revisores realizaram a seleção, extração dos dados e avaliação do risco de viés utilizando ferramentas da JBI. Foram realizadas metanálises de efeitos aleatórios utilizando a diferença de médias padronizada (SMD) como estimativa de efeito e 95% de intervalo de confiança. Como resultados, *Capítulo 1* - Oito estudos preencheram os critérios de elegibilidade e foram incluídos. Todos os estudos apresentaram risco moderado de viés. A meta-análise descreveu uma sensibilidade geral de 93,3% para os níveis de creatinina salivar e 87,5% para os níveis de ureia salivar, enquanto a especificidade geral foi de 87,1% e 83,2% para os níveis de creatinina salivar e ureia, respectivamente. *Capítulo 2* - Apenas seis estudos preencheram os critérios de elegibilidade e foram incluídos. Todos os estudos apresentaram baixo risco de viés e demonstraram redução significativa da ureia / creatinina salivar e sérica após a hemodiálise. A meta-análise demonstrou uma correlação moderada a alta entre os níveis salivares e sanguíneos de ureia ( $r: 0,79$ ) e creatinina ( $r: 0,64$ ), com nível muito baixo de certeza. *Capítulo 3* - Trinta e três estudos foram incluídos na síntese qualitativa e 31 na meta-análise. Pacientes com doença renal crônica apresentaram menor

fluxo salivar (SMD: 1.87), maior pH (SMD: 1.47) e maiores níveis de fósforo (SMD: 0.86). Somente o fluxo salivar apresentou alteração significativa após a hemodiálise (SMD: 0.61). As evidências científicas demonstraram a viabilidade do uso da saliva para verificar indicadores de função renal em alternativa ao sangue, além de confirmarem que pacientes com doença renal crônica apresentam alterações importantes nas propriedades e constituintes salivares, e que a hemodiálise é capaz de afetar os níveis salivares de fósforo, ureia e creatinina e melhorar o fluxo salivar.

**Palavras-chave:** Diálise renal. Insuficiência renal crônica. Proteínas e peptídeos salivares. Saliva.

## ABSTRACT

Chronic kidney disease is an important health problem, with an estimated prevalence of 11% of the adult population, worldwide. Patients with this disease may present changes in salivary composition, as this fluid is directly related to blood composition. The objective of this study was to assess the existing evidence regarding the relationship between the diagnosis of chronic kidney disease and salivary disorders in adult patients. In *Chapter 1* – An electronic search was performed in eight databases to verify the use of creatinine and salivary urea in the diagnosis of chronic kidney disease. Only diagnostic test studies were included. The JBI tool was used to assess the risk of bias. A meta-analysis of proportions was performed, and the GRADE tool was used to assess the certainty of the evidence of the estimates. *Chapter 2* - Eight databases were used to identify before and after studies with patients with hemodialysis disease. The JBI tool was used for the risk of bias. Meta-analyses were conducted to compare the salivary and serum correlation and to group the differences in proportion and mean of pre-and post-hemodialysis levels of urea and creatinine. The GRADE approach was used to assess the certainty of the evidence. *Chapter 3* - An electronic search was done in nine databases to locate observational clinical studies, without the restriction of year or language of publication. Two reviewers performed the selection, data extraction, and risk of bias assessment using JBI tools. Random effects meta-analyses were performed using the standardized mean difference (SMD) as the effect estimate and 95% confidence interval. As a result, Chapter 1 - Eight studies met the eligibility criteria and were included. All studies had a moderate risk of bias. The meta-analysis described an overall sensitivity of 93.3% for salivary creatinine levels and 87.5% for salivary urea levels, while the overall specificity was 87.1% and 83.2% for levels of salivary creatinine and urea, respectively. Chapter 2 - Only six studies met the eligibility criteria and were included. All studies showed a low risk of bias and demonstrated a significant reduction in salivary and serum urea/creatinine after hemodialysis. The meta-analysis demonstrated a moderate to a high correlation between salivary and blood levels of urea ( $r: 0.79$ ) and creatinine ( $r: 0.64$ ), with a very low level of certainty. Chapter 3 - Thirty-three studies were included in the qualitative synthesis and 31 in the meta-analysis. Patients with chronic kidney disease had lower salivary flow (SMD: 1.87), higher pH (SMD: 1.47), and higher levels of phosphorus (SMD: 0.86). Only salivary

flow showed a significant change after hemodialysis (SMD: 0.61). Scientific evidence has demonstrated the feasibility of using saliva to check indicators of renal function as an alternative to blood, in addition to confirming that patients with chronic kidney disease have important changes in salivary properties and constituents and that hemodialysis is capable of affecting salivary levels of phosphorus, urea, and creatinine and improve salivary flow.

**Keywords:** Renal Dialysis. Renal Insufficiency, Chronic. Saliva. Salivary Proteins and Peptides.

# **Introdução & Referencial teórico**

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## 1. INTRODUÇÃO E REFERÊNCIAL TEÓRICO

As atuais diretrizes internacionais definem doença renal crônica (DRC) como uma deterioração progressiva e crônica dos néfrons, originada por doenças que alteram a função e a estrutura do rim de forma irreversível, ao longo de meses ou anos (Álamo et al., 2011). O melhor indicador disponível para avaliação da função renal é a taxa de filtração glomerular (TFG), que corresponde à quantidade total de fluido filtrado por todos os néfrons em funcionamento por unidade de tempo (Levey et al., 2020). As diretrizes atuais classificam a função renal da seguinte forma: (1) Normal:  $TFG \geq 90 \text{ mL/min/1.73m}^2$ ; (2) Levemente reduzida: TFG entre  $60\text{--}89 \text{ mL/min/1.73m}^2$ ; (3a) Levemente a moderadamente reduzida: TFG entre  $45\text{--}59 \text{ mL/min/1.73m}^2$ ; (3b) Moderadamente a severamente reduzida: TFG entre  $30\text{--}44 \text{ mL/min/1.73m}^2$ ; (4) Severamente reduzida: TFG entre  $15\text{--}29 \text{ mL/min/1.73m}^2$ ; (5) Insuficiência renal:  $TFG < 15 \text{ mL/min/1.73m}^2$  (Webster et al., 2017). Para ser diagnosticado com DRC, o paciente precisa apresentar uma  $TFG < 60 \text{ mL/min/1.73m}^2$  por pelo menos 3 meses consecutivos (Webster et al., 2017).

Estima-se que a DRC afeta cerca de 11% a 13% da população mundial (Hill et al., 2016), sendo a 18ª causa de morte de adultos no ano de 2010 (Lozano et al., 2012) e as principais condições sistêmicas associadas ao desenvolvimento da DRC incluem diabetes, hipertensão arterial, uso de substâncias tóxicas, infecções e doenças autoimunes (Chen et al., 2019). Nas fases iniciais da DRC, os pacientes costumam ser assintomáticos e desenvolvem sintomas à medida que a doença avança, como alteração na coloração da urina, incômodo ao urinar, inchaço na face ou pernas, dor lombar, falta de apetite, ressecamento da pele, falta de ar, fraqueza, náuseas e vômitos, além de alteração na pressão arterial (Chen et al., 2019).

Devido ao declínio na taxa de filtração glomerular, ocorre o aumento de substâncias tóxicas no sangue (também chamados de toxinas urêmicas) e deficiências de compostos imunológicos, como IgA, IgM e IgG (Pallos et al., 2015). As concentrações das toxinas urêmicas aumentam à medida que a DRC progride, e pode interagir negativamente em várias funções biológicas, com efeitos deletérios principalmente no sistema cardiovascular (Barreto et al., 2014). As principais toxinas urêmicas retidas em organismos de pacientes com DRC são ADMA (dimetilarginina assimétrica), ácido úrico, fosfato inorgânico, FGF-23 (Fator de

crescimento de fibroblastos 23), PTH (paratormônio), AGEs (Produtos finais da glicação avançada), indoxil sulfato e para-cresil sulfato (Barreto et al., 2014). Além disso, pacientes com DRC apresentaram níveis elevados de substratos metabólicos na corrente sanguínea, como a creatinina e ureia. A creatinina é produzida pelas células musculares em um ritmo constante a partir da degradação da fosfocreatina para liberar a energia necessária para a função muscular, e é filtrada nos glomérulos renais antes de ser excretado pela urina (Levey et al., 2005). O índice de creatinina no sangue é o principal parâmetro usado para determinar a taxa de filtração glomerular (Pham, 2017). Enquanto a ureia é um composto orgânico nitrogenado produzido a partir da oxidação de aminoácidos nas células de mamíferos e é derivada especialmente nos hepatócitos, sendo então excretada no sangue para posterior filtração nos glomérulos renais como o principal composto orgânico da urina (Walser and Bodenlos, 1959). A concentração de ureia no sangue é um valor indireto para avaliar a função renal, sendo um parâmetro analisado para avaliar a necessidade de hemodiálise ou transplante renal (Nandan et al., 2005; Thomás et al., 2008). Outros compostos como cálcio e fósforo estão presentes em níveis elevados na corrente sanguínea de pacientes com doença renal crônica, e podem desencadear a formação de cálculos renais (Craven et al., 2008).

Algumas alterações orais também foram descritas em pacientes com diagnóstico de DRC, como xerostomia (Anuradha et al. 2015), halitose (Anuradha et al. 2015) e aumento do risco de doença periodontal (Deschamps-Lenhardt et al., 2019), além de alterações no fluxo, pH e composição salivar (Anuradha et al. 2015). Em pacientes com DRC, estudos mostraram alterações quantitativas dos constituintes salivares, como cálcio, fósforo, ureia, potássio, sódio e creatinina, com associação positiva com alterações sanguíneas das mesmas moléculas nesses pacientes (Thomás et al., 2008; Rodrigues et al., 2016). Acredita-se que a saliva possa ser uma segunda via de excreção de bioprodutos (Rodrigues et al., 2016), portanto, os componentes que se acumulam no sangue podem chegar à saliva por meio de mecanismos de difusão passiva, transporte ativo ou ultrafiltração do fluido extracelular induzida por pressão hidrostática através de junções estreitas entre as células acinares (Celec et al., 2016). Além disso, pacientes com DRC podem apresentar alterações na permeabilidade celular das glândulas salivares devido ao maior gradiente de concentração, o que facilita a

difusão de moléculas como a creatinina e a ureia (Nakahari et al., 1996). Tais alterações podem contribuir para o desenvolvimento de problemas orais (Bossola and Tazza, 2012). A redução do fluxo salivar, por exemplo, pode elevar os níveis de fosfato salivar que, por sua vez, pode predispor maior formação de cálculo dentário na cavidade oral (Epstein et al., 1980). Desequilíbrios séricos entre os íons cálcio e fósforo também podem estar intimamente relacionados à formação de cálculo (Eigner et al., 1986; Costa Filho et al., 2007) e aumento do risco de doença periodontal (Costa Filho et al., 2007; Deschamps-Lenhardt et al., 2019).

Nos últimos anos, a saliva tornou-se uma opção para monitorar indicadores biológicos em diversas doenças (Satish et al., 2014; Du et al., 2017) e as vantagens desse método são a facilidade de coleta, baixo custo, maior aceitação do paciente, e ser não-invasivo (Yoshizawa et al., 2013). Especificamente para a doença renal crônica, a saliva tem se mostrado uma ferramenta promissora para o diagnóstico dessa condição em estágios avançados. Além disso, o monitoramento da eficácia da hemodiálise é de extrema importância para determinar o prognóstico clínico do paciente e para acompanhar a regressão ou o desenvolvimento de insuficiência renal (Nandan et al., 2005), o qual é feito por meio de análise laboratorial dos compostos sanguíneos. No entanto, a coleta de sangue é um procedimento invasivo que pode levar alguns pacientes a um estado de ansiedade (Yoshizawa et al., 2013), além de possíveis infecções cruzadas (Villanueva et al., 2008). Portanto, a substituição desse procedimento por um método de coleta mais fácil, não invasivo e de baixo custo, tornam a saliva um fluido ideal para monitorar os efeitos da hemodiálise (Yoshizawa et al., 2013).

Nesse contexto, é primordial que se conheça as evidências existentes da relação entre a doença renal crônica e alterações salivares em pacientes adultos, para que a análise salivar possa ser utilizada com segurança no diagnóstico e acompanhamento desse grupo, substituindo as análises sanguíneas.

# Objetivos

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## **2. OBJETIVOS**

### **Objetivo Geral**

Avaliar e investigar por meio de revisões sistemáticas da literatura as evidências existentes quanto à relação entre o diagnóstico de doença renal crônica e alterações salivares em pacientes adultos.

### **Objetivos Específicos**

#### **Objetivo específico 1**

**Capítulo 1 – *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***

Verificar se os níveis de ureia e creatinina salivares refletem com precisão seus níveis sanguíneos para diagnosticar a doença renal crônica em adultos.

#### **Objetivo específico 2**

**Capítulo 2 – *Saliva as a tool for monitoring hemodialysis – A systematic review and meta-analysis***

Avaliar se as alterações dos níveis de ureia e creatinina do sangue também ocorrem na saliva após a hemodiálise de pacientes adultos diagnosticados com doença renal crônica.

#### **Objetivo específico 3**

**Capítulo 3 – *Alterações salivares em pacientes com doença renal crônica em hemodiálise – revisão sistemática e meta-análise***

Investigar se pacientes renais crônicos apresentaram alterações significativas no pH, fluxo e níveis de cálcio, fosfato e fosforo salivares, quando comparados a pacientes saudáveis, antes e após a realização da hemodiálise.

# ***Capítulos***

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### 3. CAPÍTULOS

#### 3.1 CAPÍTULO 1

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##### REVIEW



## 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

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### Abstract

**Objectives** To assess whether salivary urea and creatinine levels accurately reflect their serum levels in blood samples of adults to detect chronic kidney disease.

**Materials and methods** A systematic review was conducted in eight electronic databases. The protocol was registered in PROSPERO. Only diagnostic test studies were included. The JBI critical appraisal tools assessed the risk of bias. A meta-analysis of proportions was performed. The GRADE tool assessed the quality of evidence and strength of recommendation across the studies included.

**Results** Eight studies met the eligibility criteria and were included. Six studies assessed salivary urea, and six studies assessed salivary creatinine. All studies presented moderate risk of bias. The meta-analysis depicted an overall sensitivity of 93.3% (95% CI = 88.6; 97.9) for salivary creatinine levels and 87.5% (95% CI = 83.2; 91.8) for salivary urea levels, while the overall specificity was 87.1% (95% CI = 82.8; 91.3) and 83.2% (95% CI = 65.0; 101.4) for salivary creatinine and urea levels, respectively. The overall accuracy of salivary creatinine was 5.2 percentage points higher compared with salivary urea levels (90.8% vs. 85.6%). According to the GRADE tool, the analysed outcomes were classified as having low to moderate level of certainty.

**Conclusion** Compared with blood samples, salivary urea and creatinine levels presented high diagnostic values for chronic kidney disease screening, but should not be considered equivalent to levels obtained from blood at stages three, four, or five of the disease.

**Clinical significance** Chronic kidney disease patients could receive a clinically significant benefit from replacing blood with saliva for potentially monitoring renal function. Saliva collection presents greater simplicity, comfort, safety, and lower collection cost.

**Keywords** Chronic kidney disease · Saliva · Urea · Creatinine

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## **ABSTRACT**

**Objectives:** To assess whether salivary urea and creatinine levels accurately reflect their serum levels in blood samples of adults to detect chronic kidney disease.

**Materials and Methods:** A systematic review was conducted in eight databases. The protocol was registered in PROSPERO. Only diagnostic test studies were included. The JBI Critical Appraisal Tools assessed the risk of bias. A meta-analysis of proportions was performed. The GRADE tool assessed the quality of evidence and strength of recommendation across the studies included.

**Results:** Eight studies met the eligibility criteria and were included. Six studies assessed salivary urea, and six studies assessed salivary creatinine. All studies presented moderate risk of bias. The meta-analysis depicted an overall sensitivity of 93.3% (95%CI = 88.6; 97.9) for salivary creatinine levels and 87.5% (95%CI = 83.2; 91.8) for salivary urea levels, while the overall specificity was 87.1% (95%CI = 82.8; 91.3) and 83.2% (95%CI = 65.0; 101.4) for salivary creatinine and urea levels, respectively. The overall accuracy of salivary creatinine was 5.2 percentage points higher compared with salivary urea levels (90.8% vs. 85.6%). According to the GRADE tool, the analysed outcomes were classified as having low level of certainty or moderate level of certainty.

**Conclusion:** Compared with blood samples, salivary urea and creatinine presented high diagnostic values for chronic kidney disease screening.

**Clinical significance:** Chronic kidney disease patients could receive a clinically significant benefit from replacing blood with saliva for potentially monitoring renal function. Saliva collection presents greater simplicity, comfort, safety, and lower collection cost.

**Keywords:** Chronic kidney disease, saliva, urea, creatinine

## INTRODUCTION

Chronic kidney disease (CKD) is characterized by the progressive and chronic deterioration of nephrons [1]. The main causes include diabetes, arterial hypertension, use of toxic substances, infections, and autoimmune diseases, and it results in the gradual reduction of renal functions, especially excretory and regulatory functions [2]. Chronic kidney disease affects around 11% to 13% of the world population [3] and it is the 18<sup>th</sup> cause of death and rising [4].

Patients with CKD experience an irreversible decline in glomerular filtration rate (GFR) [1], leading to the increase of toxic substances in the blood and deficiencies of immunological compounds, such as IgA, IgM, and IgG [5]. Creatinine is produced by muscle cells at a steady pace from the phosphocreatine breakdown to release the energy required for muscle function. It is also filtered in the renal glomeruli before being excreted through urine [6]. Measuring creatinine excretion is the most efficient means of assessing renal glomerular filtration function. The creatinine index in the blood is the main parameter used to determine glomerular filtration rate [7], which is clinically assessed by creatinine clearance [8]. Urea is a nitrogenated organic compound produced from the oxidation of amino acids in the cells of mammals and it is formed especially in hepatocytes, and then is excreted in the blood for further filtration in the renal glomeruli as the main organic compound of urine [9]. It is an indirect value to assess renal function, need for hemodialysis, or kidney transplant [10,11].

Patients with CKD need to repeat blood analyses constantly to verify the stage of the disease, monitor the treatment, and assess the clinical prognosis [12]. However, blood collection is an invasive procedure that causes anxiety and discomfort to patients [13]. Moreover, the repeated venous puncture increases the chances of infection [14], which explains CKD patients presenting higher risks of contamination for hepatitis B and C [15].

Some oral changes have been described in patients diagnosed with CKD such as xerostomia [16], halitosis [16], and increased risk of periodontal disease [17], in addition to changes in flow, pH, and salivary composition [16]. Saliva is a mixed oral fluid from major and minor salivary glands, composed of hundreds of different proteins and thousands of peptide sequences [18]. Over the last years, saliva has become an option for monitoring

biological indicators in several diseases [19-21] and the advantages of this method are easy collection, non-invasiveness, and low cost [22]. In CKD patients, several studies showed quantitative changes of salivary constituents, such as calcium, phosphorus, urea, potassium, sodium, and creatinine with a positive association with blood changes of the same molecules in these patients [10,23-28]. However, a synthesis of the results gathered by all these studies and the level of evidence to support the use of saliva to monitor those molecular changes has not been performed yet.

Thus, the present study aimed, through a systematic review of the literature, to assess whether salivary urea (SaU) and salivary creatinine (SaCr) adequately reflect the blood levels of these molecules to monitor chronic kidney disease progression. The authors tested the following hypotheses: (1) Salivary creatinine is as reliable as blood creatinine to detect CKD; (2) Salivary urea is as reliable as blood urea to detect CKD.

## **MATERIALS AND METHODS**

### ***Protocol and registration***

This systematic review was performed according to the list of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations [29] and the Cochrane guidelines [30]. The systematic review protocol was registered in the PROSPERO database under no. CRD42018111577.

### ***Study design and eligibility criteria***

This study was a systematic review that aimed to answer the following guiding question: "Are salivary urea and salivary creatinine reliable biomarkers to monitor chronic kidney disease progression in comparison with the blood assessment of both these molecules?"

The inclusion criteria were diagnostic studies comparing salivary and blood urea or creatinine to diagnose/monitor chronic kidney disease (CKD) patients at stages 3, 4, or 5 ( $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ ), without restriction of year and publication status.

Exclusion criteria were: 1) Studies not related to the objective; 2) Studies including patients at CKD stages lower than 3 ( $\text{GFR} > 60 \text{ mL/min/1.73 m}^2$ ) or with unspecified stage;

3) Studies including patients with renal diseases other than CKD; 4) Studies that were not published in the roman alphabet; 5) Review articles, letters to the editor/editorials, personal opinions, books/book chapters, textbooks, reports, conference abstracts, and patents; 6) Completely descriptive studies; 7) Studies in animals; 8) Studies in children; and 9) Studies with high risk of bias or low methodological quality.

### ***Sources of information and search***

Embase, Latin-American and Caribbean Health Sciences Literature (LILACS), PubMed (including MedLine), SciELO, Scopus, and Web of Science databases were used as primary study sources. OpenThesis and OpenGrey were used to partially capture the "grey literature". A manual search was also performed through a systematized analysis of the reference list of the eligible articles. All steps were performed to minimize selection and publication biases.

The MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors), and Emtree (Embase Subject Headings) resources were used to select appropriate search descriptors. The Boolean operators "AND" and "OR" were used to enhance the research strategy through several combinations (Table 1). The bibliographic search ended in October 2018. The search strategy included the following descriptors: "Kidney Diseases", "Kidney Disease", "Chronic Kidney Disease", "Chronic Renal Disease", "Renal Insufficiencies", "Kidney Insufficiency", "Renal Function", "Kidney Function", "Renal Failure", "Renal Injury", "Saliva", "Salivary Creatinine", "Salivary Urea", "Salivary Biomarkers". The results obtained were exported to the EndNote Web™ software (Thomson Reuters, Toronto, Canada), in which duplicates were removed. The remaining results were exported to Microsoft Word™ 2010 (Microsoft™ Ltd, Washington, USA), in which the remaining duplicates were manually removed.

**Table 1.** Strategies for database search.

| Database                                                                                               | Search Strategy (October, 2018)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PubMed</b><br><a href="http://www.ncbi.nlm.nih.gov/pubmed">http://www.ncbi.nlm.nih.gov/pubmed</a>   | ("Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" OR "Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Function" OR "Kidney Function" OR "Renal Failure" OR "Renal Injury") AND ("Saliva" OR "Salivary Creatinine" OR "Salivary Urea" OR "Salivary Biomarkers")                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Scopus</b><br><a href="http://www.scopus.com/">http://www.scopus.com/</a>                           | ( ("Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Function" ) AND ( "Saliva" OR "Salivary Creatinine" OR "Salivary Urea" ) )<br>( ( "Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" ) AND ( "Saliva" OR "Salivary Creatinine" OR "Salivary Urea" ) )                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>LILACS</b><br><a href="http://lilacs.bvsalud.org/">http://lilacs.bvsalud.org/</a>                   | tw:("Kidney Diseases" AND "Saliva") AND (instance:"regional") AND (db:("LILACS"))<br>tw:("Renal Insufficiencies" AND "Saliva") AND (instance:"regional") AND (db:("LILACS"))<br>tw:("Kidney Insufficiency" AND "Saliva") AND (instance:"regional") AND (db:("LILACS"))<br>tw:("Kidney Diseases" AND "Salivary Creatinine") AND (instance:"regional") AND (db:("LILACS"))<br>tw:("Renal Insufficiencies" AND "Salivary Creatinine") AND (instance:"regional") AND (db:("LILACS"))<br>tw:("Kidney Insufficiency" AND "Salivary Creatinine") AND (instance:"regional") AND (db:("LILACS"))<br>tw:("Kidney Diseases" AND "Salivary Urea") AND (instance:"regional") AND (db:("LILACS"))<br>tw:("Renal Insufficiencies" AND "Salivary Urea") AND (instance:"regional") AND (db:("LILACS")) |
| <b>SciELO</b><br><a href="http://www.scielo.org/">http://www.scielo.org/</a>                           | Kidney Diseases AND Saliva<br>Renal Insufficiencies AND Saliva<br>Kidney Insufficiency AND Saliva<br>Kidney Diseases AND Salivary Creatinine<br>Renal Insufficiencies AND Salivary Creatinine<br>Kidney Insufficiency AND Salivary Creatinine<br>Kidney Diseases AND Salivary Urea<br>Renal Insufficiencies AND Salivary Urea<br>Kidney Insufficiency AND Salivary Urea                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Embase</b><br><a href="http://www.embase.com">http://www.embase.com</a>                             | ('kidney diseases' OR 'kidney disease' OR 'chronic kidney disease' OR 'chronic renal disease' OR 'renal insufficiencies' OR 'kidney insufficiency' OR 'renal function') AND ('saliva' OR 'salivary creatinine' OR 'salivary urea')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Web Of Science</b><br><a href="http://apps.webofknowledge.com/">http://apps.webofknowledge.com/</a> | ( ( "Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" OR "Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Function" ) AND ( "Saliva" OR "Salivary Creatinine" OR "Salivary Urea" ) )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>OpenGrey</b><br><a href="http://www.opengrey.eu/">http://www.opengrey.eu/</a>                       | ( "Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" OR "Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Function" ) AND ( "Saliva" OR "Salivary Creatinine" OR "Salivary Urea" )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>OpenThesis</b><br><a href="http://www.openthesis.org/">http://www.openthesis.org/</a>               | ("Kidney Disease") AND ("Saliva")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

### ***Study selection***

Study selection was performed in three phases. In the first phase, as a calibration exercise, two reviewers discussed the eligibility criteria and applied them to a sample of 20% of the studies retrieved after the initial search to determine inter-examiner agreement. After achieving a proper level of agreement ( $Kappa \geq 0.81$ ), two reviewers [RPCBR and WAV] performed a methodical analysis of all the titles of the studies, independently. The reviewers were not blind to the names of authors and journals. Titles not related to the topic were eliminated in this phase. In the second phase, the reviewers [RPCBR and WAV] read the abstracts independently for the initial application of the aforementioned exclusion criteria. Studies containing titles that met the objectives of the study but did not have abstracts available were fully read in phase three.

In the third phase, preliminary eligible studies had their full texts evaluated to verify whether they fulfilled the eligibility criteria. When both reviewers disagreed, a third reviewer [LRP] was consulted to make a final decision. Excluded studies were registered in a separate database listing the reasons for exclusion.

### ***Data collection***

After the selection, the studies were analysed and two reviewers [*Blinding*] extracted information regarding the identification of the study (author, year, location, and type of study), sample characteristics (number of patients, distribution by sex, average age, and stage of chronic kidney disease), characteristics of biological material collection and processing (method for collecting saliva and blood and type of blood and salivary analyses), biomarkers' specific results (creatinine and urea concentration in saliva and blood), and validity and reliability results (cut-off, type of statistical analysis, correlation index, specificity, sensitivity, and ROC curve). Accuracy was calculated using sensitivity and specificity estimates provided by the studies.

To ensure consistency among the reviewers, a calibration exercise was performed with both reviewers [RPCBR and WAV], in which information was extracted jointly from an eligible study. Any disagreement between the reviewers was solved through discussions, and when both reviewers disagreed, a third one [LRP] was consulted to make a final decision.

### ***Risk of individual bias of the studies***

The Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews [31] for diagnostic test studies assessed the risk of bias and the individual methodological quality of the selected studies. Two authors [RPCBR and WAV] assessed independently each domain regarding their potential risk of bias, as recommended by the PRISMA statement [29]. Each study was categorized according to the percentage of positive answers to the questions corresponding to the assessment tool. Risk of bias was considered **High** when the study obtained 49% of "yes" answers, **Moderate** when the study obtained 50% to 69% of "yes" answers, and **Low** when the study reached more than 70% of "yes" score.

### ***Summary measures and syntheses of results***

A prevalence of 10.6% was defined for pre-test probability [3]. A proportion meta-analysis was performed to estimate overall sensitivity, specificity, and accuracy of using salivary creatinine and urea concentrations to detect chronic kidney disease. The concentration of the biomarkers in saliva was compared with their concentration in blood samples, which was considered the gold standard. Results are presented as proportions and were combined using random effects. The random effects model was chosen to account for the heterogeneity between the studies. Heterogeneity was assessed with  $I^2$  statistics and classified as follows: low ( $I^2 < 25\%$ ), moderate ( $I^2 = 50\%$ ), and high ( $I^2 > 75\%$ ) [32,33]. Publication bias was not assessed because there were not more than 10 studies to be grouped in one funnel plot [34]. The Stata 15.1 (Stata Corp., Texas, USA) software was used to perform the statistical analyses.

### ***Quality of evidence collection***

Quality of evidence and strength of recommendation were assessed with the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) tool [35]. The GRADE pro GDT software (<http://gdt.guidelinedevelopment.org>) was used for summarizing the results. This assessment was based on study design, methodological limitations,

inconsistency, indirect evidence, imprecision, and other considerations. The level of certainty among the evidence identified was characterized as high, moderate, low, or very low [35].

## **RESULTS**

### ***Study selection***

During the first phase of study selection, 1,138 results were found among the eight electronic databases. After removing duplicates, 652 articles remained for the analysis of titles and abstracts, and then 17 studies were considered eligible for the full text analysis. Experts suggested one additional study. The references of the 18 potentially eligible studies were evaluated carefully and no additional article was selected, resulting in 18 studies for the full text reading. After reading the full text, 10 studies did not fulfil the inclusion criteria and were eliminated. Appendix 1 shows the studies eliminated and the reasons for exclusion. Thus, finally eight studies were selected for qualitative analysis and meta-analysis. Figure 1 reproduces the process of search, identification, inclusion, and exclusion of articles.

### ***Characteristics of eligible studies***

The studies were published between the years of 2005 and 2018 and they were performed in India [11,25,26], Argentina [28], Nigeria [27], Vietnam [7], Turkey [36] and Japan [24]. The total sample included 580 chronic kidney disease patients and 389 healthy controls. Average age ranged between 39.8 and 51.3 years among case group patients and between 25.2 and 48.2 years among control group patients (Table 2).

Saliva and blood samples were collected simultaneously in all studies [7,11,24-25-28], except for one that did not specifically clarify it [24], but all collected samples during the morning and before haemodialysis. Five studies collected unstimulated saliva samples [7,11,25,26,36] and two stimulated saliva samples [27,28]. Seven [7,11,25-28,36] eligible studies analysed saliva and blood using a colorimetric method, and one study [24] used reversed-phase liquid chromatography with tandem mass spectrometry.

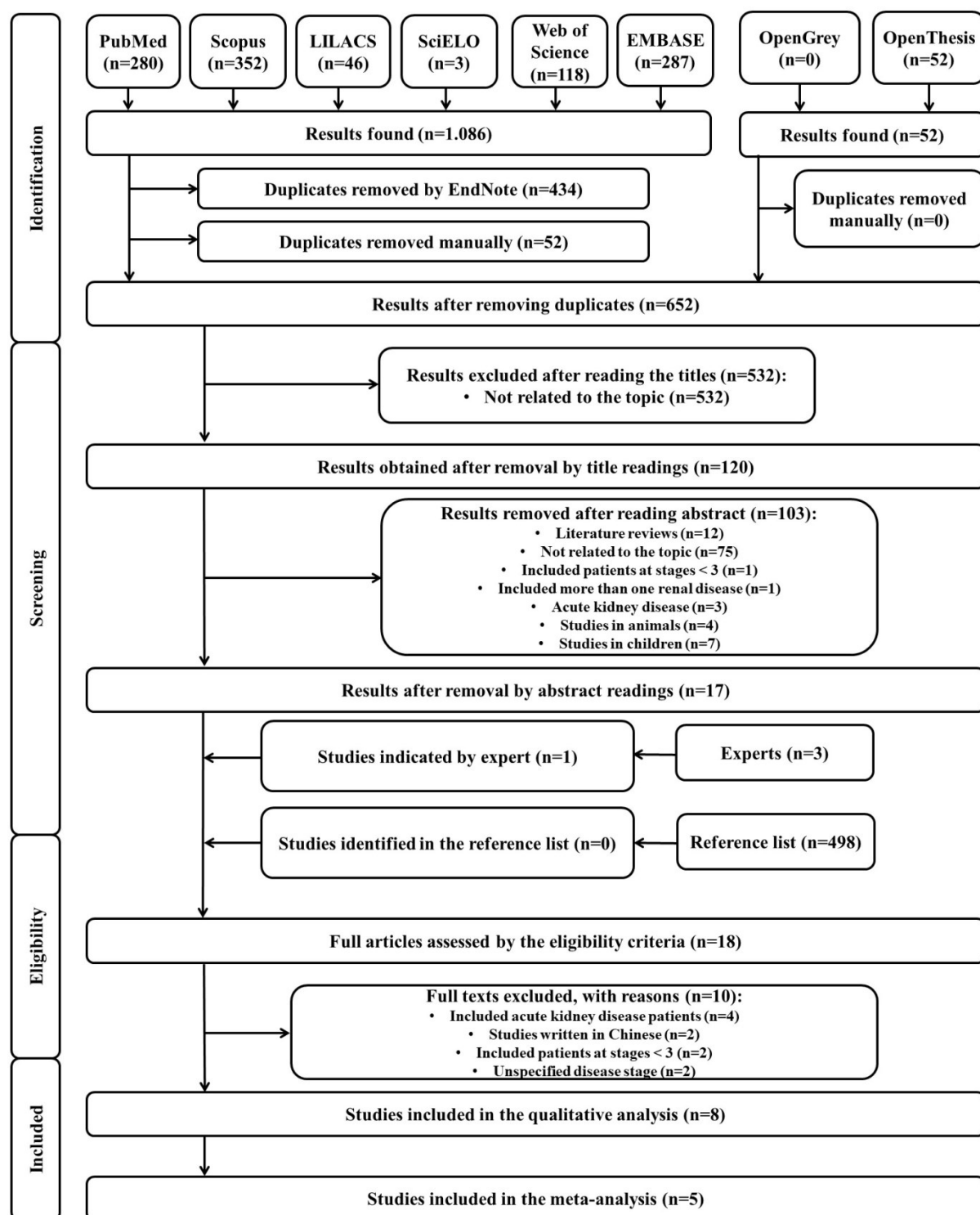


**Figure 1** - Flowchart of the process of literature search and selection, adapted from the PRISMA statement.

**Table 2** – Main characteristics of the eligible studies.

| Author, year and country of publication      | Sample (n)                                         | Mean age (years)                                   | CKD stage                                             | Saliva sampling: method / time in relation to hemodialysis                                                                                                             | Time of blood sampling in relation to saliva sampling | Type of saliva sampling                                                                                                                 | Type of blood sampling                                                                                                                                                                                                              |
|----------------------------------------------|----------------------------------------------------|----------------------------------------------------|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Nandan et al., 2005. India. [11]</b>      | Case: 20<br>(4♀ 16♂)<br>Control: 10<br>(4♀ 6♂)     | Case: 46.5<br>Control: 25.2                        | Hemodialysis patients                                 | Unstimulated saliva was collected between 9 to 11 a.m, prior to hemodialysis. All individuals were asked to spit into a plastic container.                             | Simultaneously                                        | Colorimetric (Automatic analyzer)                                                                                                       | +                                                                                                                                                                                                                                   |
| <b>Cardoso et al., 2009. Argentina. [28]</b> | Case: 154<br>(77♀ 77♂)<br>Control: 78<br>(40♀ 38♂) | +                                                  | Glomerular filtration rate <50 mL/min                 | Stimulated saliva was collected between 7 to 9 a.m. All subjects collected 3.5 mL of whole saliva by expectoration into sterile polypropylene tubes.                   | Simultaneously                                        | Colorimetric (Urea color 2R kit, Wiener Laboratory, Argentina).                                                                         | Colorimetric (Urea color 2R kit, Wiener Laboratory, Argentina).<br>In patients with end-stage renal disease showing U levels < 20.0 mmol/L, the salivary and serum assays were performed by diluting samples (1:2) in PBS solution. |
| <b>Venkatapathy et al., 2014.India. [25]</b> | Case: 105<br>(21♀ 84♂)<br>Control: 37<br>(16♀ 21♂) | Case: 47.5<br>(±15.2)<br>Control: 44.5<br>(±14.97) | Stage 4 and 5 (Glomerular filtration rate <30 mL/min) | Unstimulated saliva was collected between 9 to 11 a.m, prior to the dialysis. Two mL of whole saliva was obtained in a sterile graduated container by spitting method. | Simultaneously                                        | Colorimetric (EM360 chemistry analyzer with ISE module) using creatinine estimation kit (Swemed diagnostics) by Jaffe kinetic reaction. | Colorimetric (EM360 chemistry analyzer with ISE module) using creatinine estimation kit (Swemed diagnostics) by Jaffe kinetic reaction.                                                                                             |

|                                           |                                                   |                                                               |                                       |                                                                                                                                                                                                 |                |                                                                    |                                                         |
|-------------------------------------------|---------------------------------------------------|---------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|--------------------------------------------------------------------|---------------------------------------------------------|
| <b>Lasisi et al., 2016. Nigeria. [27]</b> | Case: 50<br>(30♀ 20♂)<br>Control: 49<br>(30♀ 19♂) | Case: 39.82<br>(±11.07)<br>Control: 39.07<br>(±7.64)          | Glomerular filtration rate <60 mL/min | Stimulated saliva was collected between 9 h to 16 h, prior to hemodialysis. Participants were asked to spit into calibrated universal plastic bottles until about 3 mL of saliva was collected. | Simultaneously | Colorimetric (Assay Kit, RANDOX Reagents, USA).                    | Colorimetric (Assay Kit, RANDOX Reagents, USA).         |
| <b>Suzuki et al., 2016. Japan [24]</b>    | Case: 11<br>(4♂ 7♀)<br>Control: 25                | +                                                             | Hemodialysis patients                 | The saliva (1 mL) was directly taken in tubes. The saliva sampling of the patients was performed within 15 min before hemodialysis and within 20 min after hemodialysis.                        | +              | Reversed-phase liquid chromatography with tandem mass spectrometry | +                                                       |
| <b>Pham, 2017. Vietnam. [7]</b>           | Case: 111<br>Control: 109                         | Case: 51.3<br>(±12.9)<br>Control: 48.2<br>(±18)               | Glomerular filtration rate <60 mL/min | Unstimulated saliva was collected between 9 to 11 a.m, prior the dialysis. Participants were asked to spit every 30 seconds into a sterile plastic cup.                                         | Simultaneously | Colorimetric (Beckman Coulter Chemistry Analyzers 5820)            | Colorimetric (Beckman Coulter Chemistry Analyzers 5820) |
| <b>Bagalad et al., 2017. India. [26]</b>  | Case: 41<br>Control: 41                           | +                                                             | Hemodialysis patients                 | Unstimulated saliva was collected by spitting method after 5 min of relaxation.                                                                                                                 | Simultaneously | Colorimetric (Semi-autoanalyzer).                                  | Colorimetric (Semi-autoanalyzer).                       |
| <b>Alpdemir et al., 2018. Turkey [36]</b> | Case: 88<br>(32♀ 56♂)<br>Control: 40<br>(16♀ 24♂) | Case: 45.8 <sup>1</sup><br>48.2 <sup>2</sup><br>Control: 43.9 | Dialysis patients                     | Unstimulated saliva was collected by spitting method after 5 min of relaxation.                                                                                                                 | Simultaneously | Spectrophotometric method.                                         | Spectrophotometric method.                              |

+Not mentioned in the article; ♀ Women; ♂ Men; <sup>1</sup>Group under peritoneal dialysis; <sup>2</sup>Group under hemodialysis.

### ***Risk of individual bias of the studies***

All eligible studies [7,11,24-28,36] presented moderate risk of bias/methodological quality. Table 3 shows detailed information on the risk of bias among the studies identified. Question 1 was considered “uncertain” in all studies as none of them explained whether the sample was obtained consecutively or randomly. Question 4 was also considered “uncertain”, because none of the studies explained whether the saliva results were interpreted without knowledge of the blood results. Question 7 was considered “uncertain” in all studies because none of them explained whether the blood results were interpreted without knowledge of the saliva results.

**Table 3** - Risk of bias assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews for Diagnostic Test Accuracy Studies. The risk of bias was classified as high when the study reached up to 49% of "yes" score, moderate when the study reached from 50% to 69% of "yes" score, and low when the study reached more than 70% of "yes" score.

| Authors                                | Q.1 | Q.2 | Q.3 | Q.4 | Q.5 | Q.6 | Q.7 | Q.8 | Q.9 | Q.10 | % of yes/risk                  |
|----------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|--------------------------------|
| Nandan <i>et al.</i> , 2005 [11]       | U   | --  | √   | U   | √   | √   | U   | √   | √   | √    | 60% yes/ moderate risk of bias |
| Cardoso <i>et al.</i> , 2009 [28]      | U   | --  | √   | U   | √   | √   | U   | √   | √   | √    | 60% yes/ moderate risk of bias |
| Venkatapathy <i>et al.</i> , 2014 [25] | U   | --  | √   | U   | √   | √   | U   | √   | √   | √    | 60% yes/ moderate risk of bias |
| Lasisi <i>et al.</i> , 2016 [27]       | U   | --  | √   | U   | √   | √   | U   | √   | √   | √    | 60% yes/ moderate risk of bias |
| Suzuki <i>et al.</i> , 2016 [24]       | U   | --  | √   | U   | --  | √   | U   | √   | √   | √    | 50% yes/ moderate risk of bias |
| Pham, 2017 [7]                         | U   | --  | √   | U   | √   | √   | U   | √   | √   | √    | 60% yes/ moderate risk of bias |
| Bagalad <i>et al.</i> , 2017 [26]      | U   | --  | √   | U   | --  | √   | U   | √   | √   | √    | 50% yes/ moderate risk of bias |
| Alpdemir <i>et al.</i> , 2018. [36]    | U   | --  | √   | U   | √   | √   | U   | √   | √   | √    | 60% yes/ moderate risk of bias |

Q.1 - Was a consecutive or random sample of patients enrolled? Q.2 - Was a case control design avoided? Q.3 - Did the study avoid inappropriate exclusions? Q.4 - Were the index test results interpreted without knowledge of the results of the reference standard? Q.5 - If a threshold was used, was it pre-specified? Q.6 - Is the reference standard likely to classify correctly the target condition? Q.7 - Were the reference standard results interpreted without knowledge of the results of the index test? Q.8 - Was there an appropriate interval between index test and reference standard? Q.9 - Did all patients receive the same reference standard? Q.10 - Were all patients included in the analysis? / √ - Yes; -- - No; U – Unclear.

### ***Specific results of the eligible studies***

Six studies compared the levels of salivary urea and blood urea [7,11,24-26,28]. In chronic kidney disease patients, the concentration of salivary urea ranged from 92.0 to 110.1

mg/dL, while blood urea ranged between 79.4 and 170.1 mg/dL. In control groups, salivary and blood urea ranged between 12.9 and 33.7 mg/dL and between 24.5 and 30.1 mg/dL, respectively. The cut-off values used in the studies were between 27.5 and 85.6 mg/dL. Compared with the blood urea, the sensitivity estimates of salivary urea were between 89.2% and 100%, and specificity between 57.8% and 100%. Table 4 shows the results of the eligible studies in detail.

Creatinine levels were assessed in six studies [7,24-27,36]. In chronic kidney disease patients, the concentration of salivary creatinine ranged between 0.4 and 2.6 mg/dL, while the concentration of blood creatinine ranged between 5.9 mg/dL and 10.5 mg/dL. In the group of healthy patients, the concentration of salivary creatinine ranged between 0.1 and 0.2 mg/dL, while the concentration of blood creatinine ranged between 0.9 and 1.2 mg/dL. The cut-off used in the studies varied from 0.2 to 0.6 mg/dL. The sensitivity of salivary creatinine as a diagnostic test, when compared with blood creatinine, ranged between 86.5% and 97.1%, while specificity varied between 85.0% and 87.2%.

### ***Synthesis of results and meta-analysis***

A total of six studies had complete information regarding sensitivity and specificity values. However, one study [28] was not considered in the meta-analyses, considering it had 100% sensitivity, specificity and accuracy values. For minimum (0%) or maximum proportions (100%) the estimate of the standard error is zero, thus it is not possible to compute Wald confidence intervals. Hence, only five studies were considered in the quantitative analyses.

Using the blood sample as the gold standard, the overall sensitivity of salivary creatinine was 93.3% (95%CI = 88.6; 97.9). This estimate was almost six percentage points higher than the sensitivity of salivary urea (Se = 87.5%; 95%CI = 83.2; 91.8) (Figure 2). As shown in Figure 3, specificity estimates were also higher for salivary creatinine than for urea. The overall specificity for creatinine was 87.1% (95%CI = 82.8; 91.3), while for urea it was equal to 83.2% (95%CI = 65.0; 101.4).

Figure 4 presents the forest plot for the accuracy analysis. The overall accuracy of using salivary creatinine to detect chronic kidney disease was 90.8% (95%CI = 87.1; 94.4),

while for salivary urea the accuracy was 85.6% (95%CI = 74.6; 96.7). The  $I^2$  estimate revealed moderate heterogeneity between findings of salivary creatinine. In contrast, almost 91% of the variation between estimates of salivary urea was attributed to heterogeneity between the studies.

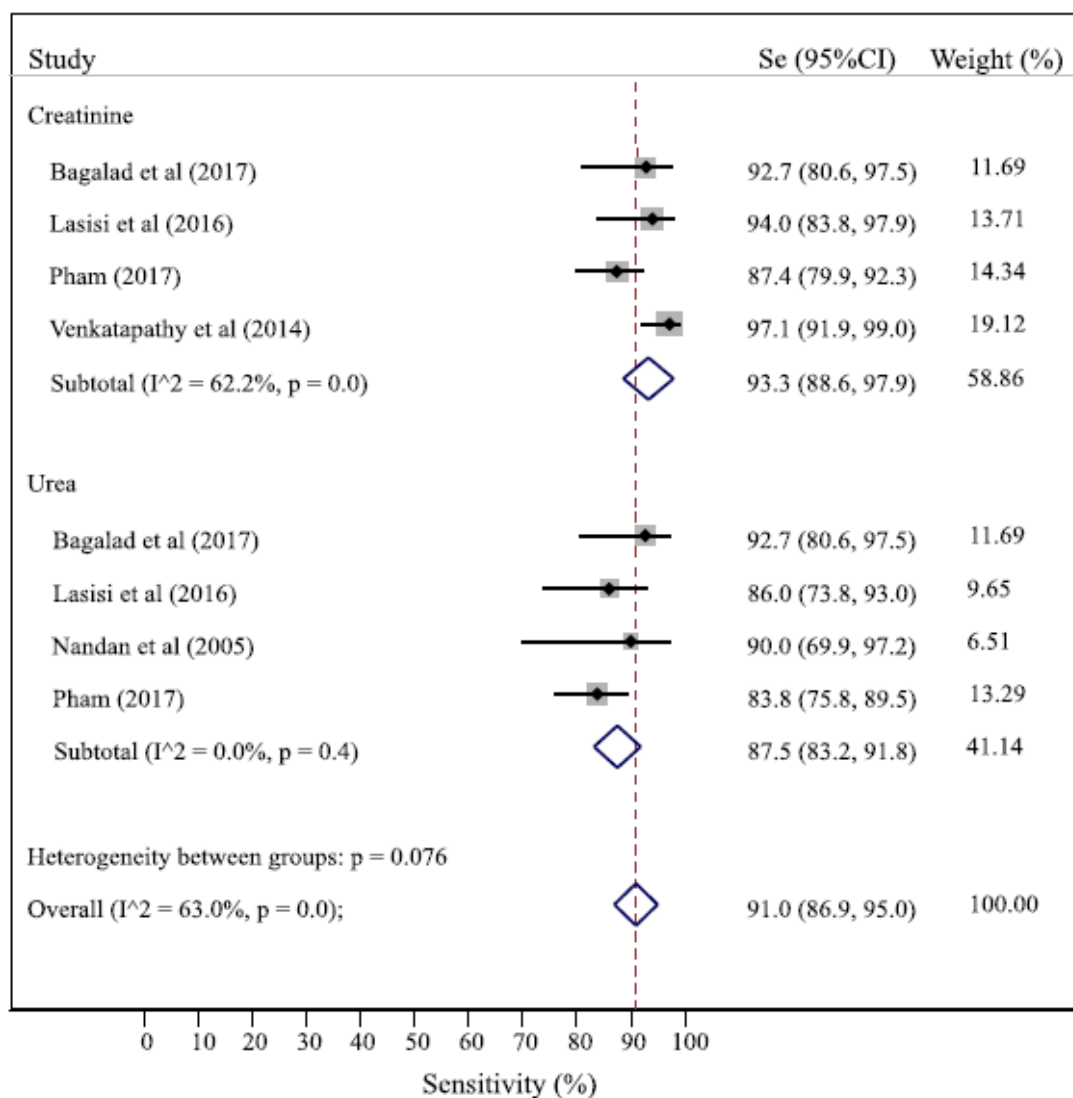


**Figure 2** - Forest plot of sensitivity estimates comparing salivary creatinine and urea concentrations with their concentration in blood. Diamonds from top to bottom represent overall sensitivity for creatinine, urea and overall groups, respectively.  $I^2$  represents a measure of heterogeneity between the studies.

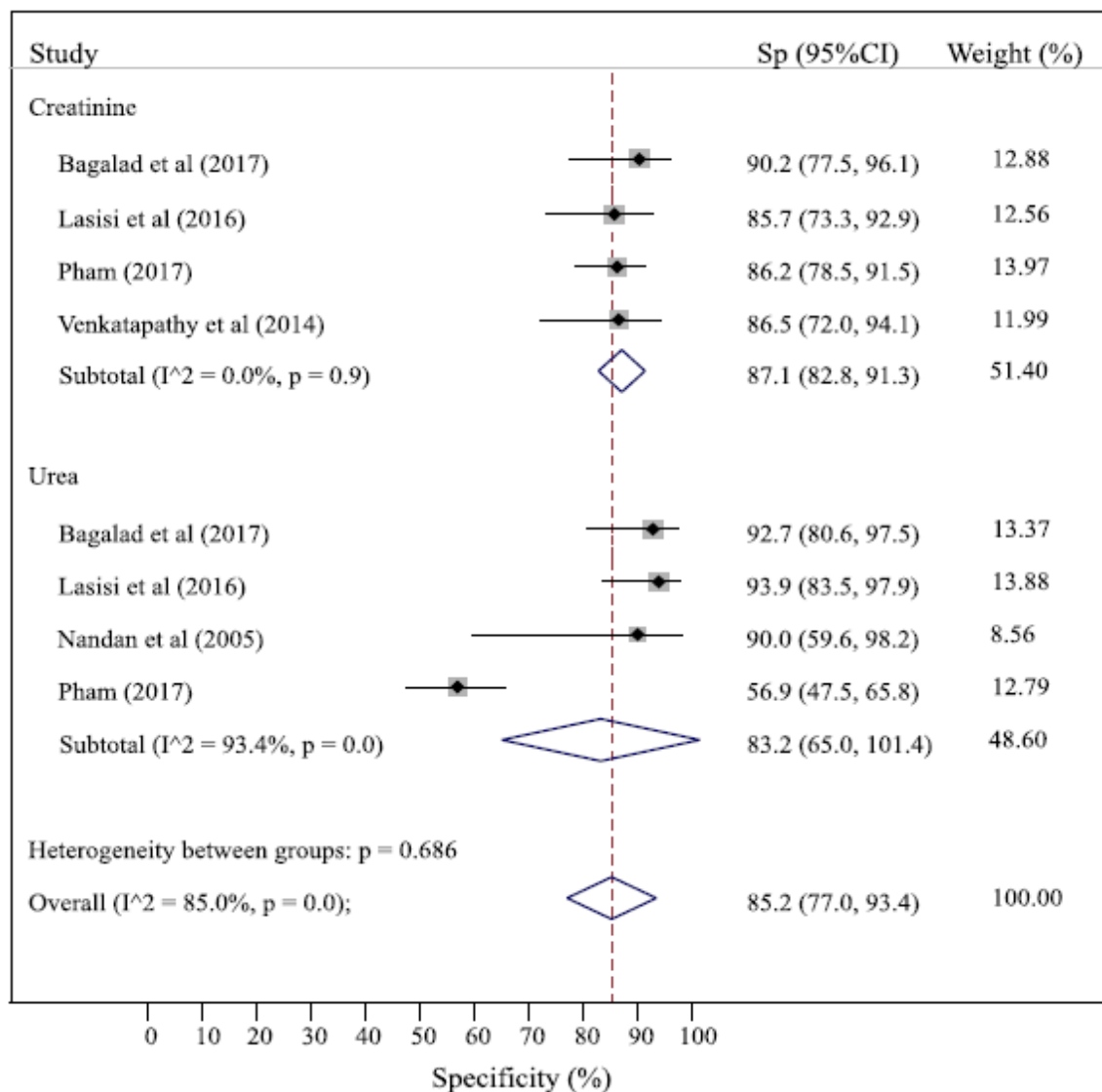


**Figure 3** - Forest plot of specificity estimates comparing salivary creatinine and urea concentrations with their concentration in blood. Diamonds from top to bottom represent overall specificity for creatinine, urea and overall groups, respectively.  $I^2$  represents a measure of heterogeneity between the studies.

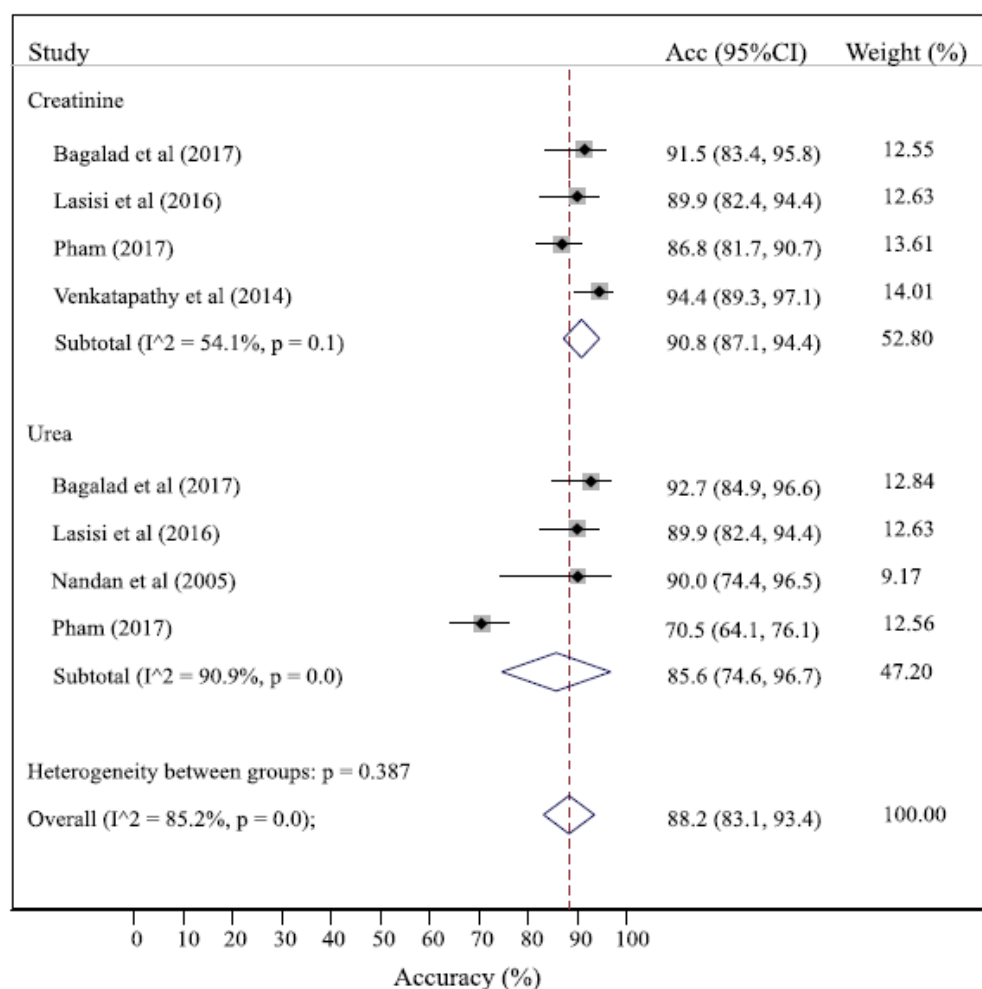


**Figure 4** - Forest plot of accuracy estimates comparing salivary creatinine and urea concentrations with their concentration in blood. Diamonds from top to bottom represent overall accuracy for creatinine, urea and overall groups, respectively.  $I^2$  represents a measure of heterogeneity between the studies.

### ***Certainty of evidence***

The GRADE tool assessed four outcomes [35]. Two outcomes were categorized as having low level of certainty, which means the true effect may be substantially different from the estimated effect. Two outcomes were categorized as having moderate level of certainty, which means the true effect is potentially close to the estimated effect, but it may be substantially different. Table 5 shows more details for each outcome.

**Table 5.** Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Summary of Findings Table for the Outcomes of the Systematic Review and Meta-Analysis.

| Outcome                           | Number of studies<br>(Number of patients) | Study design                     | Factors that may decrease certainty of evidence |              |                      |             |                  | Effect                | Effect per 1.000 patients tested | Test accuracy CoE |
|-----------------------------------|-------------------------------------------|----------------------------------|-------------------------------------------------|--------------|----------------------|-------------|------------------|-----------------------|----------------------------------|-------------------|
|                                   |                                           |                                  | Risk of bias                                    | Indirectness | Inconsistency        | Imprecision | Publication bias |                       |                                  |                   |
| <i>Salivary creatinine levels</i> |                                           |                                  |                                                 |              |                      |             |                  |                       |                                  |                   |
| True positives <sup>1</sup>       | 4 studies (461 patients)                  | case-control type accuracy study | serious <sup>a</sup>                            | not serious  | serious <sup>b</sup> | not serious | none             | 0.933 (0.886 – 0.979) | 99 (94 to 104)                   | ⊕⊕ LOW            |
| False negatives <sup>2</sup>      |                                           |                                  |                                                 |              |                      |             |                  |                       |                                  | 7 (2 to 12)       |
| True negatives <sup>3</sup>       | 4 studies (461 patients)                  | case-control type accuracy study | serious <sup>a</sup>                            | not serious  | not serious          | not serious | none             | 0.871 (0.828 – 0.913) | 779 (740 to 816)                 | ⊕⊕⊕ MODERATE      |
| False positives <sup>4</sup>      |                                           |                                  |                                                 |              |                      |             |                  |                       |                                  | 115 (78 to 154)   |
| <i>Salivary urea levels</i>       |                                           |                                  |                                                 |              |                      |             |                  |                       |                                  |                   |
| True positives <sup>1</sup>       | 4 studies (431 patients)                  | case-control type accuracy study | serious <sup>a</sup>                            | not serious  | not serious          | not serious | none             | 0.875 (0.832 – 0.918) | 93 (88 to 97)                    | ⊕⊕⊕ MODERATE      |
| False negatives <sup>2</sup>      |                                           |                                  |                                                 |              |                      |             |                  |                       |                                  | 13 (9 to 18)      |
| True negatives <sup>3</sup>       | 4 studies (431 patients)                  | case-control type accuracy study | serious <sup>a</sup>                            | not serious  | serious <sup>b</sup> | not serious | none             | 0.832 (0.650 – 1.0)   | 744 (581 to 894)                 | ⊕⊕ LOW            |
| False positives <sup>4</sup>      |                                           |                                  |                                                 |              |                      |             |                  |                       |                                  | 150 (0 to 313)    |

<sup>1</sup> patients with chronic kidney disease; <sup>2</sup> patients incorrectly classified as not having chronic kidney disease; <sup>3</sup> patients without chronic kidney disease; <sup>4</sup> patients incorrectly classified as having chronic kidney disease; <sup>a</sup>All studies presented moderate risk of bias; <sup>b</sup>I<sup>2</sup> > 50%.

## DISCUSSION

This systematic review of the literature aimed to investigate the validity of creatinine and urea in saliva concentrations compared with blood concentrations in the diagnosis of chronic kidney disease. The results presented in the meta-analysis showed high accuracy for both salivary biomarkers, thus corroborating the hypotheses that salivary creatinine and urea are an accurate method to suggest chronic kidney disease.

Kidneys are responsible for filtering blood plasma and excreting metabolic waste products to regulate the volume and composition of the extracellular fluid in the body. Chronic kidney disease is characterized by a decrease in glomerular filtration rate and consequently an increase in metabolic bioproduct concentrations in the circulatory system. According to the Renal Association, patients with GFR higher than 60 mL/min/1.73 m<sup>2</sup> should not be considered to have CKD, unless there are other markers of renal disease [37]. Thus, aiming to minimize the bias regarding CKD diagnosis, only studies involving patients with GFR < 60 mL/min/1.73 m<sup>2</sup> were considered eligible.

The increased concentration of metabolic products in the blood stream of CKD patients is extensively discussed in the literature [6,8,13,21]. The studies selected are in line with these findings, considering there were higher blood and saliva concentrations of urea and creatinine in patients diagnosed with CKD compared with the control group. Some hypotheses may be established to explain the increase in the concentration of these molecules in saliva. It is believed that saliva may be a second excretion route of bioproducts [23], thus the components that accumulate in the blood may reach saliva through passive diffusion mechanisms, active transportation, or ultrafiltration of the extracellular fluid [38]. Moreover, CKD patients may show changes in cell permeability of salivary glands due to a higher concentration gradient, which facilitates the diffusion of molecules such as creatinine and urea [39].

Compared with blood, the results found in our meta-analysis for specificity, sensitivity, and accuracy, as well as creatinine and salivary urea levels, appear to be potentially effective in suggesting chronic kidney disease. These results reinforce the existing conceptual interconnection between the salivary and blood components already established in the literature published [18-20].

The literature indicates that the concentration of urea in the blood of patients without renal impairment ranges between 13 and 43 mg/dL and these indices may increase ten-fold in patients with renal deficiency [40]. These numbers agree with the results observed in the eligible studies [7,11,25-27,36], in which blood urea ranged between 79.4 and 170.1 mg/dL in CKD patients and between 24.5 and 30.1 mg/dL in patients not diagnosed with the disease. Aligned with these numbers, the concentration levels of urea in saliva were similar to those found for blood in all eligible studies [7,11,25-27,36]. These results may be justified by the fact that the urea molecule has a low molecular weight and a small size, which would facilitate its passive diffusion in the blood stream to the small intercellular junctions of the salivary glands [40]. Additionally, the increase of urea in saliva may be noticed in the halitosis of patients with CKD, considering that urea in the saliva is degraded into ammonia ( $\text{NH}_3$ ) by enzymes present in the oral cavity (arginase and urease) [41]. Thus, assessing the amount of  $\text{NH}_3$  in the breath of chronic renal patients under hemodialysis may be a complementary tool to assess the levels of salivary urea.

Similarly, blood and salivary creatinine concentrations were higher for patients with chronic kidney disease compared with the controls. These patients show an increased concentration of creatinine in the blood stream due to the low GFR [42]. This increased concentration creates a concentration gradient that will positively help diffusing the creatinine molecules to saliva [38], which explains the high concentration of creatinine in the saliva of these patients. Another hypothesis for the relationship between salivary and blood creatinine concentrations is that CKD patients show changes in the cell permeability of salivary glands, which would facilitate the ultrafiltration of the extracellular fluid by hydrostatic pressure [43].

Several limitations in the eligible studies may justify the heterogeneity between the findings, especially those related to salivary urea accuracy. First, the studies were used in different populations with different age groups. Additionally, the eligible studies involve patients at different CKD stages in different sample proportions, which interferes directly with the concentrations found. One study by Tomás and colleagues (2014) [10] concluded that creatinine and urea concentrations increase as the disease stage becomes more severe.

To the best of our knowledge, this is the first systematic review of the literature that observed the validity and reliability of salivary biomarkers as a tool to suggest and/or monitor chronic kidney disease. The high overall estimates of sensitivity, specificity and accuracy support this. Moreover, the extensive search in different databases, without restrictions of publication year and language, and the use of the "grey literature" minimize significantly the risk of bias in the study selection. The use of GRADE [35] and The Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews [30] to assess the risk of bias and the methodological quality of the studies included, respectively, supports the accuracy with which the data of the eligible studies were collected.

This review enlightens the importance of salivary constituents for diagnosing chronic kidney disease. This is an important finding especially because saliva is easy to be collected and it presents low cost, little invasiveness, and minimum exposure of patients to contamination. Besides these advantages, the study by Cardoso et al. (2009) [28] observed that urea and creatinine levels do not vary with either the amount of saliva or the time of collection, which allows the monitoring of these biomarkers regardless of the time of the day.

### ***Limitations***

This study is not free of limitations. The first one refers to the high heterogeneity observed in the eligible studies, mainly caused by the lack of standardization in the assessment of results. Moreover, the present meta-analysis did not stratify the correlations according to different CKD levels, considering that the concentration levels of urea and creatinine may be different at the different stages of the disease [10].

Another limitation in this review is with respect to the general quality of the evidence found. According to the GRADE tool [35], two out of the four outcomes obtained low certainty level. This is primarily due to limitations in study designs, since all studies presented moderate risk of bias. Secondly, the high inconsistency observed among the studies for each outcome decreased the overall level of certainty of the evidence identified.

Thus, although the results presented are relatively consistent, they should be analysed with caution, and further studies are required to confirm truly the use of saliva as a tool for diagnosing chronic kidney disease.

## CONCLUSION

Based on a moderate level of certainty of evidence, the salivary creatinine measurement had higher accuracy compared with urea, but both seem suitable to suggest chronic kidney disease in patients at stages three, four, or five of the disease. Thus, chronic kidney disease patients could receive a clinically significant benefit from replacing or complementing blood with saliva as the biological material used for analysing renal function at specific stages of patient care.

## COMPLIANCE WITH ETHICAL STANDARDS

**Conflict of Interest:** All of the authors declare no conflict of interest.

**Funding:** No Funding.

**Ethical approval:** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent:** For this type of study, formal consent is not required.

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**Appendix 1** – Studies excluded in the reading of the full texts and the reasons for exclusion (n=10).

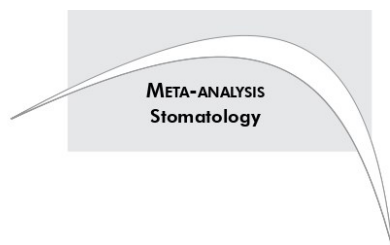
|     | <b>Study excluded</b>         | <b>Reason for exclusion</b>            |
|-----|-------------------------------|----------------------------------------|
| 1.  | <i>Lloyd et al., 1996</i>     | Included acute kidney disease patients |
| 2.  | <i>Xia et al., 2012</i>       | Study written in Chinese               |
| 3.  | <i>Zúñiga et al., 2012</i>    | Included patients at stages < 3        |
| 4.  | <i>Peng et al., 2013</i>      | Unspecified disease stage              |
| 5.  | <i>Cheng et al., 2013</i>     | Study written in Chinese               |
| 6.  | <i>Suresh et al., 2014</i>    | Included acute kidney disease patients |
| 7.  | <i>Pandya et al., 2016</i>    | Unspecified disease stage              |
| 8.  | <i>Evans et al., 2016</i>     | Included acute kidney disease patients |
| 9.  | <i>Yajamanam et al., 2016</i> | Included acute kidney disease patients |
| 10. | <i>Bilancio et al., 2018</i>  | Included patients at stages < 3        |

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## 3.2 CAPÍTULO 2



### Saliva as a tool for monitoring hemodialysis: a systematic review and meta-analysis

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**Abstract:** This study aimed to assess whether the reductions in serum urea and creatinine levels are different from the reductions in salivary urea and creatinine levels that occur after hemodialysis in chronic renal patients. The systematic review protocol was registered in the PROSPERO database. Eight databases were searched to identify pretest-posttest studies of chronic kidney disease patients undergoing hemodialysis, with no language or year restrictions. The JBI Critical Appraisal Tool was used to assess the risk of bias. Meta-analyses using random-effect models were conducted to compare salivary and serum correlations and to pooled mean and proportion differences from pre- to posthemodialysis urea and creatinine levels by subgroup analysis. The I<sup>2</sup> test was used to assess heterogeneity, and a meta-regression was performed to statistically assess correlations and differences in the pooled effects pre- and postdialysis. The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of evidence. The search resulted in 1404 records, and only six studies (n = 252 participants) fulfilled the eligibility criteria and were included. The studies were published between 2013 and 2018. All studies showed a significant reduction in both salivary and serum urea/creatinine levels. All eligible studies presented a low risk of bias. The meta-analysis shows a moderate to high correlation between salivary and blood levels of urea (r: 0.79; 95% CI: 0.56-1.00) and creatinine (r: 0.64; 95%CI: 0.16-1.00), with a very low level of certainty. The reductions in salivary urea and creatinine levels are similar to and correlated with the reductions in blood urea and creatinine levels after hemodialysis among chronic kidney disease patients.

**Keywords:** Renal Insufficiency, Chronic; Saliva; Urea; Creatinine.

### Introduction

Hemodialysis is the treatment option commonly indicated for purifying blood in patients diagnosed with advanced chronic kidney disease (CKD).<sup>1</sup> Hemodialysis is responsible for filtering toxic substrates from the bloodstream, such as creatinine, urea, and phosphorus, thus decreasing the signs and symptoms of these patients.<sup>2</sup>

The glomerular filtration rate (GFR) is an assessment of the filtering capacity of the functioning nephrons in the kidneys. GRF is a sensitive

## **Saliva as a tool for monitoring hemodialysis: a systematic review and meta-analysis**

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## **ABSTRACT**

This study aimed to assess whether the reduction of serum urea and creatinine levels are reflected in salivary levels after hemodialysis in chronic renal patients. The systematic review protocol was registered in the PROSPERO database. Eight databases were screened to identify pretest-posttest studies with chronic kidney disease patients under hemodialysis, with no language or year restriction. The JBI Critical Appraisal Tool was used to assess the risk of bias. Meta-analyses using random-effect models were conducted to compare salivary and serum correlation and to pooled mean and proportion differences from pre- to post-hemodialysis of urea and creatinine levels by subgroup analysis. The  $I^2$  test was used to assess heterogeneity and a meta-regression was performed to statistically assess correlation and differences in the pooled effects pre and post-dialysis. The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of evidence. The search resulted in 1404 records and only six studies (n=252 participants) fulfilled the eligibility criteria and were included. The studies were published between 2013 and 2018. All studies significantly show reduction of both salivary and serum urea/creatinine. All eligible studies presented a low risk of bias. The meta-analysis shows a moderate to high correlation between salivary and blood levels of urea ( $r:0.79$ ; 95%CI: 0.56-1.00) and creatinine ( $r:0.64$ ; 95%CI: 0.16-1.00), with very low level of certainty. There is a similar and correlated reduction in salivary urea and creatinine levels to the reduction found in the blood after hemodialysis in chronic kidney disease patients.

**Keywords:** Chronic kidney disease; saliva; urea; creatinine.

## INTRODUCTION

Hemodialysis is the treatment option commonly indicated for purifying blood in patients diagnosed with chronic kidney disease (CKD) in advanced stages.<sup>1</sup> Hemodialysis is responsible for filtering toxic substrates from the bloodstream such as creatinine, urea, and phosphorus, thus decreasing the signs and symptoms of these patients.<sup>2</sup>

Glomerular filtration rate (GFR) is an assessment of the filtering capacity of the functioning nephrons in the kidneys. GRF it is a sensitive method to detect and monitor changes in renal function<sup>7</sup>. Changes in GFR are a good predictor for determining the need for renal replacement therapy such as dialysis. Clearance of exogenous substances such as inulin or various radio-labelled markers is considered the gold standard for determining GFR. In addition, despite the use of creatinine and urea levels, cystatin C has been considered a candidate marker to evaluate patients with CDK and interestingly this protein can also be found and precisely quantified in saliva using the state-of-the-art mass spectrometry. Monitoring the efficacy of hemodialysis is of utmost importance for determining the clinical prognosis of the patient and for following-up on regression or the development of renal failure.<sup>3</sup> Laboratory analysis of blood is used to identify substrates in the blood, such as creatinine and urea.<sup>4</sup> However, blood collection is an invasive procedure that may lead some patients into a state of anxiety.<sup>5</sup> Moreover, the repeated venous punctures increases the chances of infection, which explains CKD patients presenting higher risks of infection from hepatitis B and C.<sup>6</sup>

The collection of saliva has been presented as an excellent alternative to collecting blood, considering that saliva is an alternative for the presence of bioproducts, containing several blood serum components.<sup>8</sup> Recent studies have presented promising results regarding the correlation of saliva and blood analytes in different clinical conditions.<sup>9-11</sup> Specifically for chronic kidney disease, saliva has been shown to be a promising tool for diagnosing this condition in early stages.<sup>12</sup> Thus, this easy collection procedure is a non-invasive and low-cost method, making saliva an optimum fluid for monitoring hemodialysis effects from home.<sup>5</sup>

In this context, the present systematic review aims to assess whether changes in the levels of urea and creatinine that occur in the serum will also occur in saliva after hemodialysis in patients diagnosed with chronic kidney disease.

## **MATERIAL AND METHODS**

### ***Protocol and registration***

This systematic review was performed according to the list of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations<sup>13</sup> and the Joanna Briggs Institute Manual<sup>14</sup>. The systematic review protocol was registered in the PROSPERO database under no. CRD42018116775.

### ***Research question and Eligibility criteria***

The performance of the study was supported by the following research question: “Is there a correlation between salivary and serum urea and creatinine levels after hemodialysis in chronic renal patients?”

#### ***Inclusion criteria***

- Population: End-stage CKD (glomerulation filtration rate  $<15$  mL/min/1.73m<sup>2</sup>) adult patients ( $> 18$  years old) under hemodialysis treatment.
- Intervention: Salivary analysis.
- Comparator: Serum analysis.
- Outcome: Assessment of urea and creatinine levels after hemodialysis.
- Study design: Clinical studies of pretest-posttest design with or without healthy patients as control group, which observed both salivary and blood levels of urea and creatinine pre- and post-hemodialysis, with no restrictions of language or year of publication.

#### ***Exclusion criteria***

- Review articles, letters to the editor/editorials, personal opinions, books/book chapters, textbooks, reports, conference abstracts, and patents.
- Studies including patients with other kidney diseases besides CKD;
- Studies with pediatric patients;

### ***Sources of information and search***

The Embase, Latin-American and Caribbean Health Sciences Literature (LILACS), PubMed/MedLine, SciELO, Scopus, and Web of Science databases were used as primary study sources. OpenThesis and OpenGrey were used to partially capture the "grey literature". Additionally, a manual search was performed in the references of the studies eligible from the electronic search. All steps were performed to minimize study selection bias.

The MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors), and Emtree (Embase Subject Headings) resources were used to select the search descriptors. In addition, synonyms and free terms were used to enhance the search. The Boolean operators "AND" and "OR" were used to enhance the search strategy through several combinations according to each database. The search terms and strategy were adapted for each database (Table 1). The bibliographic research was performed in December 2018 and updated on March 21st, 2020. The results obtained were exported to the EndNote Web™ software (Thomson Reuters, Toronto, Canada), in which duplicates were removed automatically. The remaining results were exported to Microsoft Word™ 2010 (Microsoft™ Ltd, Washington, USA), in which any remaining duplicates were removed manually.

### ***Study selection***

The studies were selected in three phases. In the first phase, as a calibration exercise, 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 achieving a proper level of agreement ( $Kappa \geq 0.81$ ), two eligibility reviewers (RPCBR and WAV) methodically analyzed the titles of the studies, independently. The reviewers were not blind to the names of authors and journals. Titles not related to the topic were eliminated in this phase. In the second phase, the reviewers (RPCBR and WAV) read the abstracts independently for the initial application of the exclusion criteria aforementioned. Those results with titles that met the objectives of the study, but did not have abstracts available, were fully analyzed in phase three.

In the third phase, the preliminary eligible studies had their full texts obtained and evaluated to verify whether they fulfilled the eligibility criteria. When reviewers disagreed, a third reviewer (LRP) was consulted to make a final decision. The studies rejected in this phase were registered separately, explaining the reasons for exclusion.

**Table 1.** Strategies for database search.

| Database                                                                                               | Search Strategy (March, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PubMed</b><br><a href="http://www.ncbi.nlm.nih.gov/pubmed">http://www.ncbi.nlm.nih.gov/pubmed</a>   | (“Kidney Diseases” OR “Kidney Disease” OR “Chronic Kidney Disease” OR “Chronic Renal Disease” OR “Renal Insufficiencies” OR “Kidney Insufficiency” OR “Renal Function” OR “Kidney Function” OR “Renal Failure” OR “Renal Injury”) AND (“Saliva” OR “Salivary Creatine” OR “Salivary Urea” OR “Salivary Biomarkers”)                                                                                                                                                       |
| <b>Scopus</b><br><a href="http://www.scopus.com/">http://www.scopus.com/</a>                           | (( "Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" ) AND ( "Saliva" OR "Salivary Creatine" OR "Salivary Urea" ))<br>tw:(“Kidney Diseases” AND “Saliva”) AND (instance:"regional") AND (db:"LILACS")                                                                                                                                                                                                                          |
| <b>LILACS</b><br><a href="http://lilacs.bvsalud.org/">http://lilacs.bvsalud.org/</a>                   | tw:(“Renal Insufficiencies” AND “Saliva”) AND (instance:"regional") AND (db:"LILACS")<br>tw:(“Kidney Insufficiency” AND “Saliva”) AND (instance:"regional") AND (db:"LILACS")<br>tw:(“Kidney Diseases” AND “Salivary Creatine”) AND (instance:"regional") AND (db:"LILACS")<br>tw:(“Renal Insufficiencies” AND “Salivary Creatine”) AND (instance:"regional") AND (db:"LILACS")<br>tw:(“Kidney Diseases” AND “Salivary Urea”) AND (instance:"regional") AND (db:"LILACS") |
| <b>SciELO</b><br><a href="http://www.scielo.org/">http://www.scielo.org/</a>                           | Kidney Diseases AND Saliva<br>Renal Insufficiencies AND Saliva<br>Kidney Insufficiency AND Saliva<br>Kidney Diseases AND Salivary Creatine<br>Hemodialise AND Saliva<br>Kidney Insufficiency AND Salivary Creatine<br>Kidney Diseases AND Salivary Urea<br>Renal Insufficiencies AND Salivary Urea<br>Kidney Insufficiency AND Salivary Urea                                                                                                                              |
| <b>Embase</b><br><a href="http://www.embase.com">http://www.embase.com</a>                             | ('kidney diseases' OR 'kidney disease' OR 'chronic kidney disease' OR 'chronic renal disease' OR 'renal insufficiencies' OR 'kidney insufficiency' OR 'renal function' OR 'kidney function' OR 'renal failure' OR 'renal injury') AND ('saliva' OR 'salivary creatine' OR 'salivary urea' OR 'salivary biomarkers')                                                                                                                                                       |
| <b>Web Of Science</b><br><a href="http://apps.webofknowledge.com/">http://apps.webofknowledge.com/</a> | (( "Kidney Diseases" OR "Kidney Disease" OR "Chronic Kidney Disease" OR "Chronic Renal Disease" OR "Renal Insufficiencies" OR "Kidney Insufficiency" OR "Renal Function" ) AND ( "Saliva" OR "Salivary Creatine" OR "Salivary Urea" ))                                                                                                                                                                                                                                    |

### ***Data collection***

The following information was extracted from the studies selected: Study identification (author, year, location), sample characteristics (number of patients in each study, distribution by sex, average age), sample collection and processing characteristics (saliva collection method, collection time of the biological material, type of salivary and blood analysis, type of statistical analysis), and specific results (concentrations of salivary and blood urea, concentrations of salivary and blood creatinine, percentage of post-hemodialysis reduction, main conclusions). In case of incomplete or insufficient information, the corresponding author was contacted via e-mail. There were no language restrictions, but articles other than English or Portuguese, have been translated for proper data extraction.

To ensure consistency among reviewers, training was performed with both reviewers, in which information was extracted jointly from an eligible study. The disagreements between the reviewers were solved through discussion and consensus. When this was not possible, a third reviewer (LRP) was consulted to make a final decision.

### ***Risk of individual bias of the studies***

The Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews for quase-experimental studies<sup>15</sup> assessed the risk of bias and the individual quality of the studies selected. The tool for quase-experimental studies was chosen because it deals with the evaluation of pretest-posttest studies where the participants are not randomized.<sup>16</sup>

Two authors (RPCBR and WAV) assessed independently each domain regarding their potential risk of bias, as recommended by the PRISMA statement<sup>12</sup>. Any disagreement between the reviewers was solved through discussions on the topics assessed and when reviewers disagreed, a third reviewer (LRP) was consulted to make a final decision.

The risk of bias was ranked as High when the study reached 49% of "yes" score, Moderate when the study reached from 50% to 69% of "yes" score, and Low when the study reached over 70% of "yes" score.

### ***Summary measures and syntheses of results***

To summarize the data, a descriptive analysis of the findings was performed. The effectiveness of the salivary measure in comparison to serum values was evaluated using meta-analysis. To compare salivary and serum agreement, a meta-analysis was conducted of correlation according to correlation ( $r$ ) values available for each study. Standard errors and confidence interval (CI 95%) of correlation were estimated to perform the meta-analysis. To compare salivary and serum concentrations of urea and creatinine, a subgroup meta-analysis was conducted evaluating the pooled mean and proportion differences from pre- to post-hemodialysis results. Only articles with data from salivary and serum concentrations were included in the meta-analysis of each renal function indicator to ensure proper comparison of pooled estimates using the same samples. The measures described in mg/dL were converted to mmol/L using the MediCalc tool (<http://www.scymed.com/>) to standardize the data<sup>17</sup>. To compare salivary and serum concentrations of urea and creatinine in the same scale, the results of potential changes in the mean concentration were presented as a standard mean difference with Hedges correction ( $g$ ) and the conversions were performed using the formulas presented by Borenstein et al. (2009)<sup>18</sup>. Additionally, a meta-regression was performed to statistically assess differences in the pooled effects estimated ( $g$ ; and proportion). The meta-analysis of all outcomes was performed using fixed- and random-effect models. The selection of each effect, either random or fixed, was based on the presence of heterogeneity ( $P < 0.05$ , chi-square or  $I^2 > 50\%$ ). When this occurred, the random-effects model was preferred<sup>19</sup>. Moreover, salivary and serum percentage reductions were measured for each renal function indicator and the pooled effects were estimated.

### ***Certainty of Evidence***

Certainty of evidence were assessed with the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) tool<sup>20</sup>. The GRADE pro GDT software (<http://gdt.guidelinedevelopment.org>) was used for summarizing the results. This assessment was based on study design, risk of bias, inconsistency, indirect evidence, imprecision, and other considerations. The certainty of evidence was characterized as high, moderate, low, or very low<sup>20</sup>.

## RESULTS

### *Study selection*

During the first phase of study selection, 1404 results were found distributed in eight electronic databases, including the grey literature. After removing the duplicates, 745 results remained for analysis of titles and abstracts. After applying eligibility criteria to the titles and abstracts, only eight results were eligible for full-text analysis. The references of the eight potentially eligible studies were carefully assessed and one additional study was selected, resulting in nine studies for full-text reading. After reading the full text, the studies of Khanum et al. (2017)<sup>3</sup>, Suzuki et al. (2016)<sup>21</sup> and Chen et al. (2020)<sup>22</sup> were excluded for not performing blood analysis after hemodialysis. Thus, six studies<sup>23-28</sup> were selected for the qualitative analysis. Figure 1 reproduces the process of search, identification, inclusion, and exclusion of articles.

### *Characteristics of eligible studies*

The studies were published between 2013 and 2018 and they were performed in China<sup>23</sup>, India<sup>24</sup>, Finland<sup>25</sup>, Bulgaria<sup>26</sup>, Italy<sup>27</sup>, and Turkey<sup>28</sup>. The total sample included 252 chronic kidney disease (CKD) patients under hemodialysis. Only one study presented a control group with healthy participants (n=40)<sup>28</sup>. The average age of the sample ranged from 43.9 to 60.66. Men prevailed in all the eligible studies containing sex data.

The saliva and blood samples were collected simultaneously in five studies<sup>23,24,26-28</sup>, before and after hemodialysis. The study by Bilancio et al. (2018)<sup>26</sup> also collected blood and saliva during hemodialysis. The collection of saliva samples was unstimulated in four studies<sup>23,25-27</sup> and stimulated in two studies<sup>23,25</sup>. Saliva and blood were analyzed with the

colorimetric method in four eligible studies<sup>23-26</sup>. The study by Chen et al. (2016)<sup>25</sup> also observed the relationship between salivary urea concentration and ammonia in the breath of CKD patients. Table 2 shows detailed information about each eligible study.

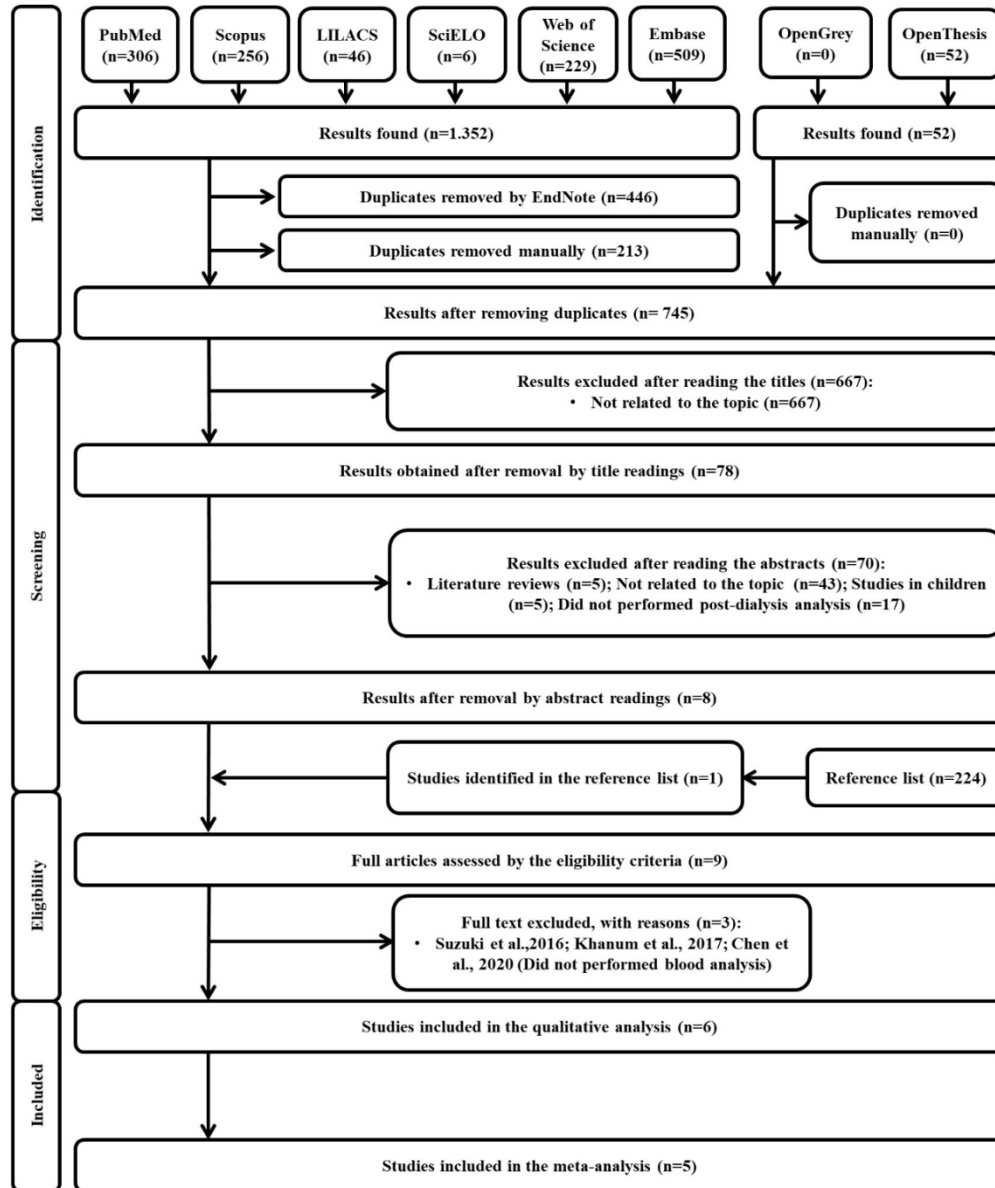


**Figure 1.** Flowchart of the process of literature search and selection adapted from the PRISMA statement.

**Table 2** - Summary of the main characteristics of the eligible studies.

| Author, year, and location                              | Sample (n)                                               | Mean age in years (SD)                                | Saliva collection method                                                                                                 | Time of blood collection relative to saliva collection | Type of salivary analysis                 | Type of blood analysis                                  | Statistical analysis                                                     |
|---------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------|
| Cheng <i>et al.</i> , 2013. China <sup>23</sup>         | 47                                                       | 48.0 (13.5)                                           | Stimulated saliva was collected (2ml) using the spitting method before and after dialysis.                               | Simultaneously                                         | Automatic analyzer (colorimetric method). | Automatic analyzer (colorimetric method).               | Student's t test, paired t test, and Pearson's correlation analysis.     |
| Seethalakshmi <i>et al.</i> , 2014. India <sup>24</sup> | 30 (16♂ 14♀)                                             | 50.33                                                 | Unstimulated whole saliva was collected (about 5 ml) using the spitting method before and after dialysis.                | Simultaneously                                         | Automatic analyzer (colorimetric method). | Automatic analyzer (colorimetric method).               | Paired t test analysis.                                                  |
| Chen <i>et al.</i> , 2016. Finland <sup>25</sup>        | 12 (8♂ 4♀)                                               | 52.41                                                 | Stimulated saliva was collected after 1 minute by chewing a paraffin pellet 1 minute before, during, and after dialysis. | Simultaneously                                         | Colorimetric method.                      | Photometric enzymatic method.                           | Spearman's rank correlation test.                                        |
| Alpdemir <i>et al.</i> , 2018. Turkey <sup>28</sup>     | Dialysis Patients: 88 (32♀ 56♂)<br>Healthy: 40 (16♀ 24♂) | Dialysis Patients: 45.8 (13.3)<br>Healthy: 43.9 (8.5) | Unstimulated saliva was collected using the spitting method after 5 min of relaxation.                                   | Simultaneously                                         | Spectrophotometric method.                | Spectrophotometric method.                              | Student's t test, paired t test, and Pearson's correlation analysis.     |
| Bilancio <i>et al.</i> , 2018. Italy <sup>27</sup>      | 5                                                        | +                                                     | Saliva samples were collected using a synthetic swap (Salivette, Sarstedt, Germany).                                     | 1-2 minutes before                                     | Urease/NADH method for urea.              | Automated biochemistry and commercially available kits. | Student's t test, simple correlation coefficient, and linear regression. |

|                                                         |                 |                  |                                                                                                                                           |                |                                                                    |                                                                    |                                                                                                 |
|---------------------------------------------------------|-----------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------|----------------|--------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Nogalcheva <i>et al.</i> , 2018. Bulgaria <sup>26</sup> | 70 (32♀<br>38♂) | 60.66<br>(14.46) | The subjects were instructed to spit saliva every minute for about 5 minutes without causing prior stimulation of the salivary secretion. | Simultaneously | UV kinetic method for urea and colorimetric method for creatinine. | UV kinetic method for urea and colorimetric method for creatinine. | Descriptive statistics, Phi and Cramer's V nominal associations, and Pearson's chi-square test. |
|---------------------------------------------------------|-----------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------|----------------|--------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|

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+ Not cited by the authors; ♀ - Female; ♂ - Male.

### ***Specific results of the eligible studies***

All eligible studies<sup>23-28</sup> assessed the levels of urea. In the saliva analysis pre-dialysis, the concentration of urea ranged from 15.85 mmol/L to 46.89 mmol/L, while in the saliva analysis post-dialysis, the concentration ranged from 5.94 mmol/L to 46.78 mmol/L. The differences pre- and post-dialysis ranged from 0.3% to 68%. When blood was analyzed, urea ranged from 21.24 mmol/L to 43.9 mmol/L before dialysis and from 6.4 mmol/L to 14.8 mmol/L after dialysis. Three<sup>23,25,27</sup> studies found strong correlation between blood urea and salivary urea, and one study<sup>27</sup> showed moderate correlation. The others two studies<sup>23,25</sup> did not perform correlation statistics (Table 3).

Four eligible studies<sup>23,24,26,28</sup> assessed the levels of creatinine. In the saliva analysis pre-dialysis, the concentration of creatinine ranged from 0.6363 mg/dL to 1.13 mg/dL, while in the saliva analysis post-dialysis, the concentration ranged from 0.34 mg/dL to 0.6343 mg/dL. The differences pre- and post-dialysis ranged from 0.4% to 70%. When blood was analyzed, creatinine ranged from 7.24 mg/dL to 11.28 mg/dL before dialysis and from 2.99 mg/dL to 4.12 mg/dL after dialysis. The differences in blood creatinine pre- and post-dialysis ranged from 31% to 72%. The differences in blood creatinine pre- and post-dialysis ranged from 52% to 64%. One study<sup>23</sup> observed a strong correlation between serum and salivary creatinine, while one study<sup>28</sup> found a low correlation. The other studies<sup>24,26</sup> did not perform correlation statistics (Table 4).

### ***Risk of individual bias of the studies***

All eligible studies<sup>23-28</sup> presented a low risk of bias. Item 4 was considered 'No' for four eligible studies<sup>23-26</sup> due to lack of a control group. Item 5 was considered 'Uncertain' for all studies because they did not make it clear how many pre-posttest measurements were performed<sup>23-28</sup>. Item 6 was considered 'Not Applicable' for all studies<sup>23-28</sup> because the posttests were performed immediately after hemodialysis, with no follow-up. Table 5 shows detailed information on the risk of bias of the studies included.

**Table 3** - Main results of the eligible studies investigating urea levels.

| Authors                                          | Mean Concentration of SaU pre-dialysis in mmol/L (SD) | Mean Concentration of SaU post-dialysis (SD) | Difference (%) | Mean concentration of SU pre-dialysis in mmol/L (SD) | Mean concentration of SU post-dialysis in mmol/L (SD) | Difference (%) | r            | Conclusion                                                                                                                                                                                                  |
|--------------------------------------------------|-------------------------------------------------------|----------------------------------------------|----------------|------------------------------------------------------|-------------------------------------------------------|----------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cheng <i>et al.</i> , 2013 <sup>23</sup>         | 28.33 (±7.53)                                         | 9.91 (±4.21)                                 | 65%            | 28.54 (± 5.85)                                       | 10.57 (± 4.22)                                        | 63%            | 0.909        | There was a strong correlation (r=0.90, p<0.001) between blood urea and salivary urea.                                                                                                                      |
| Seethalakshmi <i>et al.</i> , 2014 <sup>24</sup> | 15.85 (± 4.99)                                        | 6.73 (± 2.62)                                | 58%            | 22.03 (± 5.46)                                       | 8.52 (± 2.69)                                         | 62%            | <sup>a</sup> | Urea levels in serum and saliva were significantly lower after hemodialysis than before hemodialysis.                                                                                                       |
| Chen <i>et al.</i> , 2016 <sup>25</sup>          | 16.92 (± 9.73)                                        | 5.94 (± 3.48)                                | 65%            | 21.67 (± 5.64)                                       | 6.73 (± 2.21)                                         | 69%            | 0.77         | There was a strong correlation (r=0.77, p<0.001, n=69) between blood urea and salivary urea.                                                                                                                |
| Alpdemir <i>et al.</i> , 2018 <sup>28</sup>      | 44.9 (± 21.10)                                        | 24.7 (± 12.42)                               | 45%            | 43.9 (± 14.96)                                       | 14.8 (± 7.78)                                         | 66%            | 0.58         | Urea levels in serum and saliva were significantly lower after hemodialysis than before hemodialysis (p<0.001). This study showed a moderate correlation (r=0.58, p<0.001) between blood and salivary urea. |
| Bilancio <i>et al.</i> , 2018 <sup>27</sup>      | 24.6 (± 5.52)                                         | 7.8 (± 2.28)                                 | 68%            | 23.2 (± 1.30)                                        | 6.4 (± 1.51)                                          | 72%            | 0.96         | The changes in saliva concentrations paralleled the changes in plasma concentrations for urea.                                                                                                              |
| Nogalcheva <i>et al.</i> , 2018 <sup>26</sup>    | 46.89                                                 | 46.78 (± 23.47)                              | 0.3%           | 21.24                                                | 14.71                                                 | 31%            | <sup>a</sup> | There was a statistically significant reduction in blood urea levels before and after dialysis (p=0.000). However, there was no statistically significant reduction in salivary urea levels (p=0.240).      |

<sup>a</sup> Variable investigated by the author; SaU – Salivary Urea; SU – Serum Urea.

**Table 4 - Main results of the eligible studies investigating creatinine levels.**

| Authors                                           | Mean concentration of SaCr pre-dialysis in mg/dL (SD) | Mean concentration of SaCr post-dialysis in mg/dL (DS) | Difference (%) | Mean concentration of SCr pre-dialysis in mg/dL (SD) | Mean concentration of SCr post-dialysis in mg/dL (SD) | Difference (%) | Correlation (r) | Conclusion                                                                                                                                                                                                         |
|---------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------|----------------|------------------------------------------------------|-------------------------------------------------------|----------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cheng <i>et al.</i> , 2013. <sup>23</sup>         | 1.13 (± 0.4)                                          | 0.34 (± 0.1)                                           | 70%            | 11.28 (± 1.98)                                       | 4.01 (± 1.48)                                         | 64%            | 0.87            | Creatinine levels in serum and saliva were significantly lower after hemodialysis than before hemodialysis, and a high correlation (r=0.87, p<0.01) were observed between blood and salivary creatinine.           |
| Seethalakshmi <i>et al.</i> , 2014. <sup>24</sup> | 0.89 (± 0.47)                                         | 0.639 (± 0.34)                                         | 29%            | 8.68 (± 2.77)                                        | 4.12 (± 1.48)                                         | 53%            | <sup>a</sup>    | Creatinine levels in serum and saliva were significantly lower after hemodialysis than before hemodialysis.                                                                                                        |
| Alpdemir <i>et al.</i> , 2018. <sup>28</sup>      | 0.66 (± 0.5)                                          | 0.43 (± 0.23)                                          | 35%            | 7.24 (± 2.5)                                         | 2.99 (± 1.06)                                         | 59%            | 0.38            | Creatinine levels in serum and saliva were significantly lower after hemodialysis than before hemodialysis (p<0.001). This study showed a low correlation (r=0.38, p<0.001) between blood and salivary creatinine. |
| Nogalcheva <i>et al.</i> , 2018. <sup>26</sup>    | 0.6363                                                | 0.6343                                                 | 0.4%           | 8.31                                                 | 4.02                                                  | 52%            | <sup>a</sup>    | There was a statistically significant reduction in blood creatinine levels before and after dialysis (p=0.000). However, there was no statistically significant reduction in salivary creatinine levels (p=0.065). |

<sup>a</sup> The authors did not perform this analysis; SaCr – Salivary creatinine; SCr – Serum creatinine.

**Table 5** - Risk of bias assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews for Quasi-experimental studies<sup>14</sup>.

| Authors                                           | Q.1 | Q.2 | Q.3 | Q.4 | Q.5 | Q.6 | Q.7 | Q.8 | Q.9 | % yes/risk     |
|---------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----------------|
| Cheng <i>et al.</i> , 2013 <sup>23</sup>          | √   | √   | √   | x   | U   | N/A | √   | √   | √   | 75% / low risk |
| Seethalakshmi <i>et al.</i> , 2014. <sup>24</sup> | √   | √   | √   | x   | U   | N/A | √   | √   | √   | 75% / low risk |
| Chen <i>et al.</i> , 2016 <sup>25</sup>           | √   | √   | √   | x   | U   | N/A | √   | √   | √   | 75% / low risk |
| Alpdemir <i>et al.</i> , 2018 <sup>28</sup>       | √   | √   | √   | √   | U   | N/A | √   | √   | √   | 88% / low risk |
| Bilancio <i>et al.</i> , 2018 <sup>27</sup>       | √   | √   | √   | √   | U   | N/A | √   | √   | √   | 88% / low risk |
| Nogalcheva <i>et al.</i> , 2018 <sup>26</sup>     | √   | √   | √   | x   | U   | N/A | √   | √   | √   | 75% / low risk |

Q1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)? Q2. Were the participants included in any comparisons similar? Q3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? Q4. Was there a control group? Q5. Were there multiple measurements of the outcome both pre and post the intervention/exposure? Q6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? Q7. Were the outcomes of participants included in any comparisons measured in the same way? Q8. Were outcomes measured in a reliable way? Q9. Was appropriate statistical analysis used? √ - yes; × - no; U – Unclear.

### ***Synthesis of results and meta-analysis***

Five studies were selected for quantitative assessment in at least one meta-analysis. Table 3 and Table 4 summarize all values of concentration, proportion differences, and the correlation (r) used to perform meta-analysis for each outcome. The study of Nogalcheva *et al* (2018)<sup>26</sup> was not included in any meta-analysis, since did not present standard deviation values to calculate standard errors for differences properly, or the correlation coefficient (r).

Bioproducts from salivary samples showed different magnitudes of correlation. Urea collected from saliva were similar to the serum values. According to the pooled correlation coefficient from the meta-analysis of urea correlation, there is a high correlation value (r: 0.79; 95%CI: 0.56-1.00). Only two studies showed data for creatinine correlation, presenting moderate correlation with high confidence interval (r: 0.64; 95%CI: 0.16-1.00). Data from all correlation coefficients estimated are presented in the Figure 2.

Mean-difference and proportion differences subgroup meta-analysis and the meta-regression does not show statistical differences between salivary and serum differences in renal function indicators from pre- to post-hemodialysis. When urea concentration reduction was analysed<sup>23-25,27,28</sup>, the serum urea values showed a standardized mean difference (g) of 3.37 mmol/L (g: 3.00; 95%CI: 2.25-4.50), which was greater than the salivary values (g: 1.95; 95%CI: 2.14 – -0.81). However, there is no statistical differences between serum and salivary values. The meta-regression analysis did not show statistical significance (p=0.157);

thus, the source of bioproducts did not explain possible heterogeneity in mean concentration reduction. Moreover, the same pattern was observed for the percentage reduction, considering the pooled reduction of 65.6% (95%CI: 57.7% – 73.6%) for serum and 58.6% (95%CI: 49.3% – 67.8%) for salivary urea concentration pre- to post-hemodialysis. The meta-regression analysis also did not show statistical significance ( $p=0.251$ ). Figure 3 show all estimates of urea indicators of renal function considering the salivary and serum samples of each study.

Only three studies<sup>23,24,28</sup> allowed for proper calculation of the salivary and serum mean concentrations and the subsequent standard errors for creatinine estimates. The results of salivary and serum creatinine mean, and proportion reductions were even more similar than urea and there was no difference in either g or the percentage of reduction between pre- and post-hemodialysis results. Salivary g reduction of creatinine concentration was 0.56 (g:0.56; 95%CI: 0.03 – 1.08), and serum values presented almost the same reduction at 0.58 (g: 0.58; 95%CI: -2.28 – 6.02). There was no statistical significance in the meta-regression as well ( $p=0.571$ ). Considering proportion of reduction, a higher value was evident in serum reduction (60.7%; 95%CI: 51.3 – 70.1) than in saliva (45.4%; 95%CI: 18.2 – 72.6) but was not a statistical difference. In agreement, meta-regression analysis showed no statistical significance ( $p=0.405$ ). Figure 4 shows the summary of meta-analysis for creatinine concentration and proportion differences.

### ***Certainty of identified evidence***

The GRADE approach<sup>20</sup> was used to assess the certainty of the summary evidence of the correlation of salivary and serum levels of urea and creatinine (Table 6). Both summary estimates presented a very low level of certainty. The analysis of the certainty of evidence started as "low" because it only included observational studies. Subsequently, inconsistency and imprecision downgraded the certainty by one and two levels, respectively. Inconsistency was judge by the  $I^2$  test of each analysis and the imprecision was judged by the number of participants and by the confidence interval of the estimates.

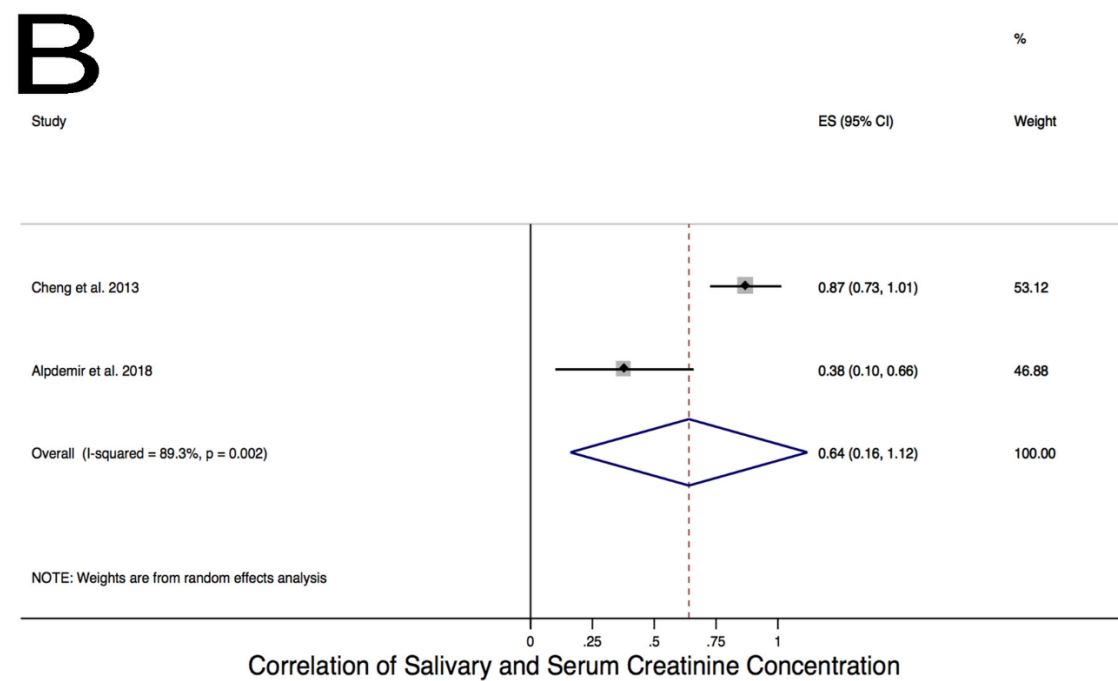
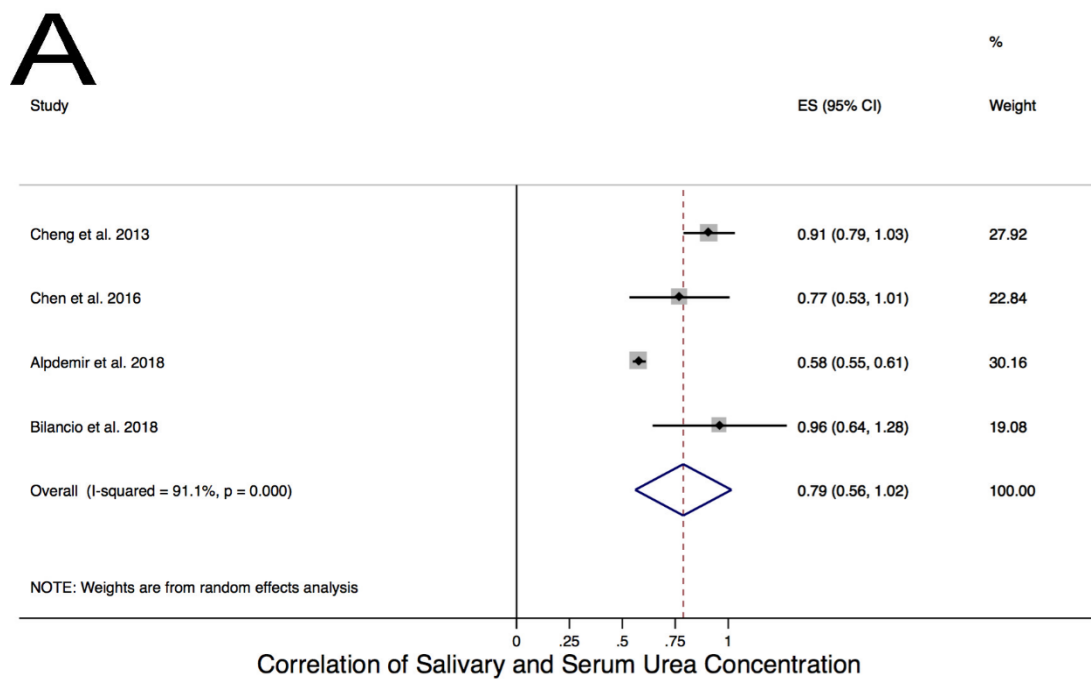


**FIGURE 2.** Forest plot of the correlation between salivary and serum (A) urea and (B) creatinine concentration.

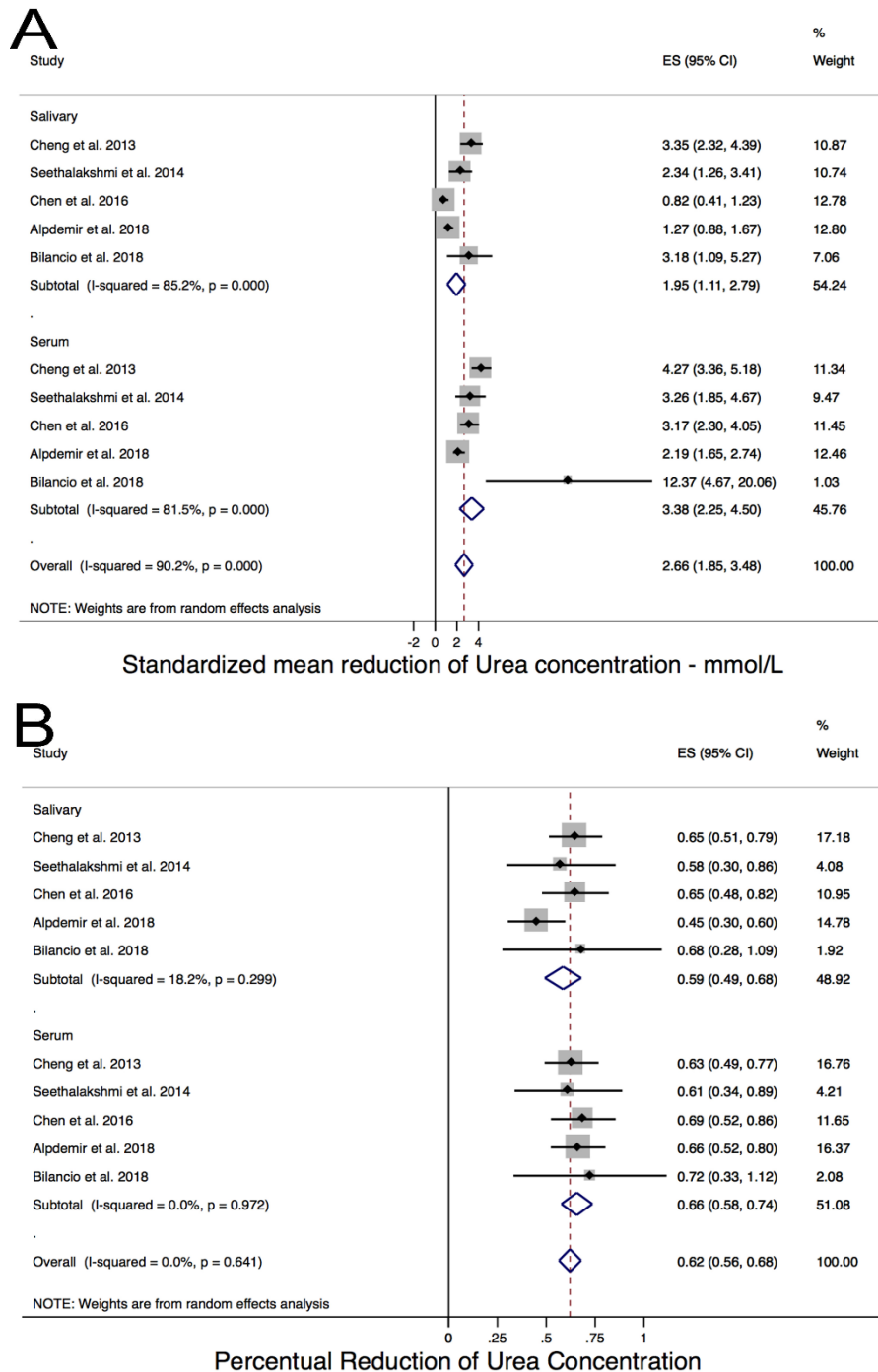


**FIGURE 3. (A)** Forest plot of the difference in urea concentrations from pre- to post-hemodialysis meta-analysis of Hedges standard mean difference (g) of urea concentration. **(B)** Forest plot of the subgroup meta-analysis of the percentage reduction of urea concentration from pre- to post-hemodialysis. Weights are from fixed effects analysis.

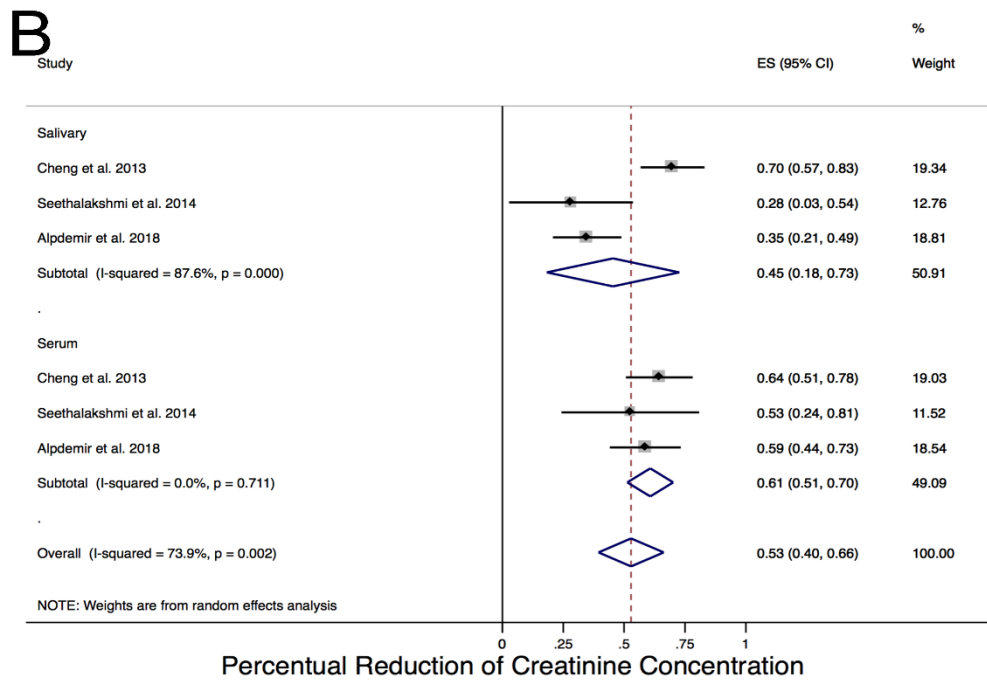
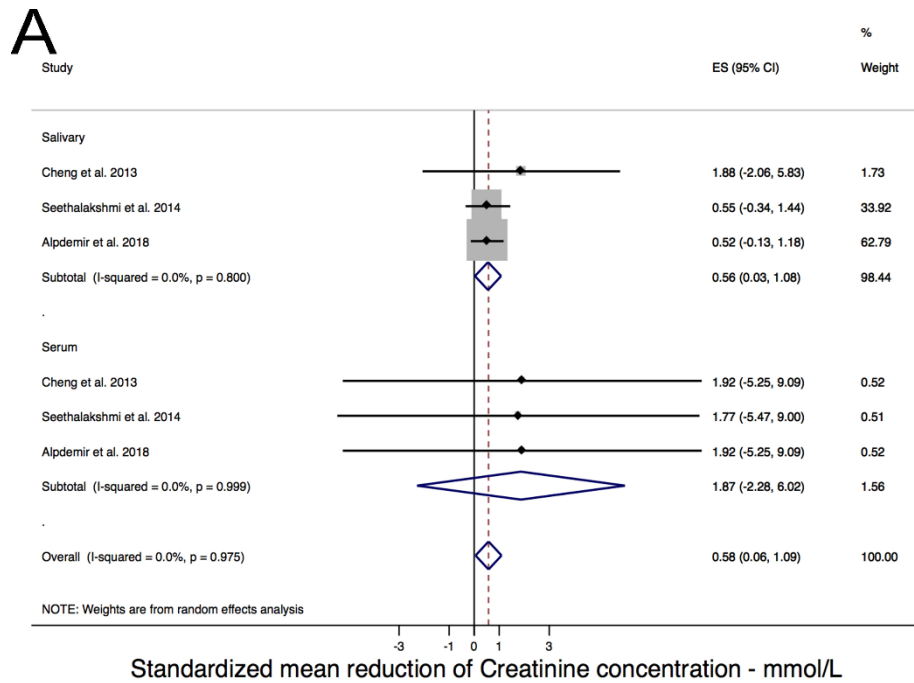


**FIGURE 4.** (A) Forest plot of the subgroup meta-analysis of Hedges standard mean difference (g) of creatinine concentration from pre- to post-hemodialysis. Weights are from random effects analysis. (B) Forest plot of the subgroup meta-analysis of the percentage reduction of creatinine concentration from pre- to post-hemodialysis. Weights are from fixed effects analysis.

**Table 6.** Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Summary of Findings Table for the Outcomes of the Systematic Review and Meta-Analysis.

| Quality Assessment                                                         |                          |                            |                      |                          |                           |                    | Summary of Results     |                                       | Importance      |          |
|----------------------------------------------------------------------------|--------------------------|----------------------------|----------------------|--------------------------|---------------------------|--------------------|------------------------|---------------------------------------|-----------------|----------|
| Number of studies                                                          | Study Design             | Methodological Limitations | Inconsistency        | Indirectness             | Imprecision               | Publication Biases | Number of participants | Effect                                | General Quality |          |
| <b>Outcome 1: Correlation between saliva and serum – Urea levels</b>       |                          |                            |                      |                          |                           |                    |                        |                                       |                 |          |
| 4                                                                          | pretest-posttest studies | Not serious <sup>a</sup>   | Serious <sup>b</sup> | Not serious <sup>c</sup> | Very serious <sup>d</sup> | none               | 152                    | <i>r</i> : 0.79<br>(95%CI: 0.56-1.00) | ⊕<br>VERY LOW   | Critical |
| <b>Outcome 2: Correlation between saliva and serum – Creatinine levels</b> |                          |                            |                      |                          |                           |                    |                        |                                       |                 |          |
| 2                                                                          | pretest-posttest studies | Not serious <sup>a</sup>   | Serious <sup>b</sup> | Not serious <sup>c</sup> | Very serious <sup>d</sup> | none               | 135                    | <i>r</i> : 0.64<br>(95%CI: 0.16-1.00) | ⊕<br>VERY LOW   | Critical |

**a** – All studies presented low risk of bias.

**b** – The I<sup>2</sup> was high (>75%) - Downgraded by one level.

**c** - Evidence came from studies with the population suitable for PICO.

**d** - Total number of participants is less than 400 and there is wide confidence interval in the effect estimates - Downgraded by two levels.

#### **GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

## DISCUSSION

This systematic literature review aimed to investigate the use of salivary components for monitoring the efficacy of hemodialysis in chronic kidney disease (CKD) patients. The meta-analysis results confirmed a reduction in urea and creatinine salivary indicators from pre- to post-hemodialysis. Despite saliva not presenting the same magnitude of the reduction observed in serum measures, there was not a statistical difference between the two approaches.

Hemodialysis is a procedure indicated for patients with glomerular filtration rate (GFR) lower than 15 ml/min/1.73m<sup>2</sup>,<sup>29</sup> in which the excess of metabolic products in the blood is filtered by diffusion through a superpermeable membrane, simulating an artificial kidney<sup>1</sup>. Controlling the efficacy of the procedure is crucial, considering it is essential to ensure the quality of life of individuals with renal impairment. In the present review, the efficacy of hemodialysis was assessed with creatinine and urea indicators pre- and post-hemodialysis, as suggested in the literature<sup>1</sup>. All eligible studies<sup>23-28</sup> showed a significant reduction in urea and creatinine levels in both blood and saliva after hemodialysis, reinforcing the importance of this procedure for controlling the signs and symptoms of CKD patients.

Urea is a nitrogenated organic compound produced from the oxidation of amino acids, especially in the liver<sup>30</sup>. The normal rates of urea in the blood and saliva are 30-40 mg/dL and 12-70 mg/dL, respectively, and these values are used as an indirect form of assessing renal function<sup>3</sup>. Several studies observed a positive correlation between blood and salivary urea indicators, in which increased levels of urea in the blood were also high in saliva<sup>8,31,32</sup>. The present meta-analysis showed a significant reduction in urea indicators in both saliva (g: -1.45; 95%CI: -2.14 – -0.81) and blood (g: -3.00; 95%CI: -4.12 – -1.88), without statistical difference between them. This means that the reduction of urea molecules in the blood is similar to the reduction of urea in saliva. Also, the meta-analysis showed a high correlation value between salivary and serum levels of urea. These results may be explained by the molecular correlation that exists between these fluids. Urea is a molecule of small size and low weight, and it easily passes through the intercellular junctions of salivary glands by passive diffusion<sup>33</sup>. Thus, once the concentration of urea in the blood decreases, fewer urea molecules are filtered to saliva, consequently reducing the levels of salivary urea.

However, urea indicators may be modified by bacteria related to dental caries and periodontitis, as well as enzymes present in saliva (arginase and urease), which degrade

urea in ammonia ( $\text{NH}_3$ )<sup>34</sup>. This is common in CKD patients<sup>27</sup> and it consequently masks the actual levels of urea in saliva. Thus, assessing the amount of  $\text{NH}_3$  in the breath of chronic renal patients under hemodialysis may be a complementary tool to assess the levels of salivary urea.

Creatinine levels are used to determine the GFR; these levels are high in CKD, indicating a lowered GFR<sup>1</sup>. Similar to the results obtained for urea, the present meta-analysis showed a reduction in creatinine levels post-hemodialysis in saliva and blood, with moderate correlation between them. Although the reduction in creatinine in blood levels was more extensive than the salivary indicators, the meta-regression did not find significant differences between both fluids, indicating that the reduction of creatinine molecules in the blood is similar to the reduction in saliva. A potential explanation for the reduction in salivary indicators is that after hemodialysis the blood creatinine indicators are reduced, and there is not a concentration gradient that affects positively the diffusion of creatinine molecules from blood to saliva, decreasing the passage of creatinine to the salivary flow<sup>35</sup>.

Although all of the eligible studies<sup>23-28</sup> presented a low risk of bias, some limitations may explain the heterogeneity obtained in the meta-analysis. First, there was a lack of detailed data for the patients analyzed, such as age, race, sex, and other systemic diseases associated with CKD. Moreover, the eligible studies<sup>23-28</sup> do not precisely confirm the GFR of the patient when comparing blood and saliva; the GFR may interfere directly with creatinine and urea indicators and with the effects of hemodialysis.

Nonetheless, this is the first systematic review of the literature that observed the potential use of salivary biomarkers as a tool for monitoring the efficacy of hemodialysis in chronic renal patients. The meta-analysis of the data obtained from the studies also represents a strength of this review, as, which provides greater consistency to the results obtained. Moreover, the extensive search in different databases, without restricting the year and using the "grey literature", significantly minimizes the risk of bias in the study selection. Using the GRADE approach<sup>20</sup> and The Joanna Briggs Institute Critical Appraisal tools to assess the certainty of the summary evidence and the methodological quality of the studies, respectively, shows the rigor of data collection of the eligible studies.

According to Dawes and Siqueira (2011)<sup>36</sup>, many plasma proteins enter saliva via gingival crevicular fluid, and for this reason saliva can be considered an important tool for monitoring patients with CKD. We find strong support for our hypothesis, since the

amount of urea and creatinine in saliva and plasma were measured in health patients and CKD patients before and after dialysis. The amount of urea (mmol/L) and creatinine (umol/l) in serum were  $13.8 \pm 3.25$ ;  $43.9 \pm 14.96$ ;  $14.8 \pm 7.78$  and  $85.7 \pm 14.14$ ;  $640.1 \pm 221.88$ ;  $252.2 \pm 94.58$ , for control group, before and after hemodialysis, respectively. In addition, the amount of urea (mmol/L) and creatinine (mmol/l) in saliva were  $21.1 \pm 11.21$ ;  $44.9 \pm 21.10$ ;  $27.4 \pm 12.42$  and  $37.2 \pm 26.52$ ;  $58.4 \pm 45.08$  and  $38.1 \pm 21.21$  for control group, before and after hemodialysis, respectively. Even with the presence of proteases in the oral cavity, the relative difference between the groups shows that salivary urea and creatinine are abundant, and that saliva testing may be valuable in CKD patient follow up. In addition, when comparing salivary creatinine and urea concentrations with their concentration in blood, our previous study described the sensitivity of 93.3% (95% CI = 88.6; 97.9) for salivary creatinine levels and 87.5% (95% CI = 83.2; 91.8) for salivary urea levels, while the overall specificity was 87.1% (95% CI = 82.8; 91.3) and 83.2% (95% CI = 65.0; 101.4) for salivary creatinine and urea levels, respectively<sup>12</sup>. Another factor that should be analyzed is the absence of data related to the oral health of the study participants, considering that the presence of oral diseases may interfere with the biomarker values analyzed.

The results from this meta-analysis reaffirm the role of saliva as a promising tool for monitoring patients in advanced stages of CKD. Patients with kidney diseases require constant and regular follow-ups and may require lifelong treatment. According to the National Kidney Foundation, CKD can be divided in 5 stages (1- Kidney damage with normal or increased GFR to 5- Kidney failure). Stage 5 patients are treated with hemodialysis; however, for patients between stages 1 and 4, very close follow up is required to estimate the disease progression, and for evaluation and treatment plans for possible complications. One of the treatments for patients in level 4 is the peritoneal dialysis, which can be done at home. Thus, replacing the blood collection with saliva collection to verify urea and creatinine levels may be beneficial in countless aspects, such as cost reduction, easy at-home collection, and decreased patient anxiety. Also, the literature reports that patients with CKD have a higher flow rate after hemodialysis (0.8 mL/min), compared to (0.4 mL/min) prior to hemodialysis, but despite of this hyposalivation scenario, saliva is still considered an alternative method for CKD patients follow up<sup>3</sup>. Additionally, given that saliva collection is a less invasive method for collecting biological material than blood collection, using saliva would decrease the risk

of infection to which patients are exposed during blood collection; this is positive, keeping in mind that the immunity of these patients is often low due to the renal problems potentially presenting secondary diseases.

Thus, the present study provides relevant and essential information that opens avenues for further studies to be performed with greater methodological rigor to adjust the GRF equation to validate the use of saliva as a diagnostic tool and as a monitoring method for kidney disease patients.

### ***Limitations***

This study is not free of limitations. The first limitation is the low number of studies included. Additionally, the eligible studies showed a high heterogeneity caused mainly by the lack of standardization in the assessment of results. Another limitation in this review is the general quality of the evidence found. According to the GRADE approach<sup>20</sup>, the summary estimates obtained very low level of certainty. This is primarily due to the design of the studies included, considering observational studies already start at lower levels. Secondly, the high inconsistencies observed among the studies for each outcome and the wide confidence interval of the summary estimates downgraded the certainty of evidence by two levels. Thus, these results should be interpreted with caution and more studies should be performed in the future.

Thus, despite the promising results, they should be analyzed with caution and further studies with an improved design (diagnostic accuracy studies) are required to confirm the use of saliva as a tool for monitoring the efficacy of hemodialysis in CKD patients and to validate a mathematical formula that establishes the GFR through saliva.

### **CONCLUSION**

There is a reduction in salivary urea and creatinine levels in comparison to the reduction found in the blood after hemodialysis in chronic kidney disease patients. As a clinical outcome, the present study provides relevant and essential information that could serve as bases for an innovative study to be performed with greater methodological rigor to adjust the glomerular filtration rate (GRF) equation to validate the use of saliva as a diagnostic tool and follow-up method for kidney disease patients.

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### 3.3 CAPÍTULO 3

*Artigo a ser enviado para publicação no periódico Archives of Oral Biology*

**Alterações salivares em pacientes com doença renal crônica em hemodiálise –  
revisão sistemática e meta-análise.**

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## **Alterações salivares em pacientes com doença renal crônica em hemodiálise – revisão sistemática e meta-análise.**

### **RESUMO**

**Objetivos:** Verificar as alterações no fluxo salivar e na composição iônica pelo pH, concentração de cálcio, fosfato e fósforo salivar de pacientes com doença renal crônica (DRC) em comparação a pacientes saudáveis e investigar a influência da hemodiálise nestes parâmetros. **Metodologia:** A busca bibliográfica foi realizada em nove bases de dados a fim de localizar estudos clínicos observacionais, sem restrição de ano ou idioma de publicação. Dois revisores realizaram a seleção, extração dos dados e avaliação do risco de viés utilizando ferramentas da JBI. Foram realizadas metanálises de efeitos aleatórios utilizando a diferença de médias padronizada (SMD) como estimativa de efeito e 95% de intervalo de confiança. **Resultados:** Trinta e três estudos foram incluídos na síntese qualitativa e 31 na meta-análise. Pacientes com doença renal crônica apresentaram menor fluxo salivar (SMD: -1.73; IC 95% = -2.14; -1.31), maior pH (SMD: 1.57; IC 95% = 1.11; 2.03) e maior concentração de fósforo (SMD: 0.86; IC 95% = 0.63; 1.09) na saliva. Somente o fluxo salivar e o pH apresentaram alterações significativas após a hemodiálise, sendo o fluxo aumentado (SMD: 0.53; IC 95% = 0.25; 0.81) e o pH reduzido (SMD: -0.53; IC 95% = -0.88; -0.19) após o tratamento. **Conclusão:** Pacientes com DRC apresentam redução de fluxo salivar e aumento do pH e da concentração de fósforo na saliva, sem diferença nos níveis de cálcio e fosfato. Ademais, a hemodiálise é capaz de aumentar o fluxo salivar de pacientes submetidos a este tratamento.

**Palavras-chave:** Eliminação salivar. Hemodiálise. Insuficiência renal crônica. Proteínas e peptídeos salivares. Saliva.

### **INTRODUÇÃO**

A doença renal crônica (DRC) é caracterizada pela degeneração estrutural e funcional dos rins (Kidney Disease: Improving Global Outcomes, 2013) de forma crônica e progressiva (Álamo, 2011). A severidade da DRC pode ser classificada em estágios de acordo com a taxa de filtração glomerular (TFG) e do nível de proteinúria (albumina/creatinina) (KDIGO, 2013). A DRC apresenta prevalência mundial entre 11 a 13% (Hill et al., 2016), sendo considerada um problema de saúde global por ser um fator importante de morbidade e mortalidade entre doenças crônicas não notificadas (Eckardt et al., 2013; GBD Chronic Kidney Disease Collaboration, 2020).

Indivíduos com DRC em estágios avançados necessitam de terapias que reponham a função renal (Abdulla et al., 2012). Neste contexto, existem disponíveis tratamentos dialíticos (hemodiálise e diálise peritoneal) e o transplante renal (KDIGO, 2013). Entre eles, a hemodiálise é a mais amplamente utilizada (Tomás et al., 2008), visando filtrar eletrólitos plasmáticos em altas concentrações, especialmente hipercalcemia e acidose metabólica (Himmelfarb and Ikizler, 2010) e também normalizar o volume circulatório através da eliminação do excesso de fluidos do organismo (Abdulla et al., 2012).

Cerca de 90% dos pacientes com DRC apresentam sinais e sintomas orais (de Rossi and Glick, 1996; Costa Filho et al., 2007), como xerostomia, halitose, paladar metálico, estomatite urêmica, mucosite, glossite, hiperplasia gengival secundária à terapia medicamentosa e lesões da mucosa oral, principalmente placas brancas e ulcerações (Kho et al., 1999; Kennedy and Linden, 1999; Antoniadis et al., 2006; Chen et al., 2019). Pacientes com DRC frequentemente também apresentam alterações no fluxo e composição salivar (Anuradha et al. 2015; Khanum et al., 2017).

A taxa de fluxo salivar em pacientes com DRC geralmente é reduzida em comparação a pacientes saudáveis (Kho et al., 1999). Além disso, a saliva destes pacientes pode apresentar maiores concentrações de ureia, sódio, fosfato, tiocianato e potássio, níveis reduzidos de cálcio, pH aumentados e capacidade tampão diminuída (Gavalda et al., 1999; Martins et al., 2006; Tomás et al., 2008; Rodrigues et al., 2019). As alterações salivares estão relacionadas com disfunções orais (Bossola and Tazza, 2012). A concentração do fosfato salivar fica elevada com a redução do fluxo salivar, o que está relacionado com processo de remineralização (Homann et al., 2005) e maior formação de cálculo dentário (Epstein et al., 1980). O aumento da concentração sérica dos íons cálcio e fósforo se refletem paralelamente na concentração salivar devido ao mecanismo de transporte dos íons cálcio e fósforo em células acinosas, o que está relacionado com a formação de cálculo dental (Eigner et al., 1986; Costa Filho et al., 2007) e aumento do risco de doença periodontal (Costa Filho et al., 2007; Deschamps-Lenhardt et al., 2019). Considerando que a decisão compartilhada é um modelo desejável na tomada de decisões da clínica odontológica (Reissmann et al., 2019), a compreensão dos efeitos da DRC no fluxo salivar, pH e composição iônica da saliva pode ser fundamental no planejamento do tratamento odontológico. Isto pode permitir o estabelecimento de diagnósticos, prescrições medicamentosas, orientações de saúde oral adequadas e um plano de tratamento para uma odontologia personalizada ao paciente com DRC (Costa Filho et al., 2007; Pham and Le, 2018).

Neste contexto, é de extrema importância prover evidências de qualidade sobre a relação entre a DRC e alterações salivares nos pacientes diagnosticados com a doença e que estão em hemodiálise, bem como que se verifique a ação do tratamento dialítico na saliva destes pacientes, logo após a realização do procedimento. Assim, a presente revisão sistemática objetiva avaliar as alterações no fluxo, pH, e níveis de cálcio, fosfato e fósforo salivar em pacientes com DRC e investigar a influência da hemodiálise nestes parâmetros.

## **MATERIAL E MÉTODOS**

### **Registro do protocolo**

O protocolo desta revisão sistemática foi descrito de acordo com as diretrizes PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) (Shamseer et al., 2015) e registrado na base de dados PROSPERO (<http://www.crd.york.ac.uk/PROSPERO>) sob o número [cego]. Esta revisão sistemática foi reportada seguindo as diretrizes PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) (Page et al., 2020) e conduzida de acordo com as normas do Manual JBI para síntese de evidência (Aromataris and Munn, 2020).

### **Pergunta de pesquisa e critérios de elegibilidade**

Esta revisão sistemática objetivou responder duas “perguntas norteadoras”, que foram desenhadas seguindo o acrônimo PECO (População, Exposição, Comparador e *Outcome* - desfecho): 1) “Pacientes com doença renal crônica em estágio terminal e que realizam hemodiálise apresentam alterações no fluxo, pH e níveis de cálcio, fosfato e fósforo salivar quando comparados a pacientes saudáveis?” e 2) “Uma sessão de hemodiálise é capaz de alterar o fluxo, pH, e níveis de fosfato, fósforo e cálcio da saliva de pacientes com DRC?”

#### **Pergunta 1:**

- População: Pacientes adultos (>18 anos);
- Exposição: Doença renal crônica (DRC) e que realizam hemodiálise (GFR < 15 ml/min/1.73m<sup>2</sup>);
- Comparador: Pacientes adultos saudáveis;
- *Outcome* (desfecho): Apresentação de alterações no fluxo, pH, e níveis de fosfato, fósforo e cálcio salivar;
- Desenho do estudo: Estudos observacionais (caso-controle ou transversal controlado).

#### Pergunta 2:

- População: Pacientes adultos (>18 anos) com doença renal crônica (DRC);
- Exposição: Hemodiálise (GFR < 15 ml/min/1.73m<sup>2</sup>);
- Comparador: Parâmetros salivares (fluxo, pH, e níveis de fosfato e cálcio) antes da diálise;
- Outcome (desfecho): Alterações no fluxo, pH, e níveis de fosfato, fósforo e cálcio salivar após a diálise;
- Desenho do estudo: Estudos antes e depois, controlados (com pacientes saudáveis) ou não-controlados.

Não foram aplicadas restrições em relação ao idioma ou ao ano de publicação para nenhuma das perguntas norteadoras.

#### ***Critérios de exclusão***

- Revisões de literatura, cartas ao editor/editoriais, opiniões pessoais, livros/capítulos de livro, relatos de caso/série de casos, estudos piloto, resumos de congresso e patentes;
- Estudos com sobreposição de resultados/amostra;
- Estudos com pacientes pediátricos;
- Estudos que não coletam a saliva total;
- Estudos incluindo pacientes com outras doenças renais que não a DRC.

#### **Fontes de informação e busca**

As pesquisas eletrônicas foram conduzidas utilizando as bases de dados MedLine (via PubMed), Scopus, LILACS, SciELO, Web of Science, Embase e LIVIVO. As bases OpenThesis e OpenGrey foram utilizadas para capturar parcialmente a "literatura cinzenta". Os recursos MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors) e Emtree (Embase Subject Headings) foram usados para selecionar os descritores de busca. Além disso, sinônimos e termos livres compuseram a busca. Os operadores booleanos "AND" e "OR" foram usados para aprimorar a estratégia de pesquisa por meio de diversas combinações. As estratégias de buscas em cada base de dados foram confeccionadas respeitando suas respectivas normas de sintaxe (Tabela 1). Os resultados obtidos nos bancos de dados primários foram inicialmente exportados para o software EndNote Web™ (Thomson Reuters, Toronto, Canadá) para catalogação e remoção de registros duplicados. Os registros da “literatura cinzenta” foram exportados

para o Microsoft Word (Microsoft <sup>TM</sup>, Ltd, Washington, EUA), onde as duplicatas foram removidas manualmente.

**Tabela 1.** Estratégias de busca nas bases de dados.

| Database                                                                                        | Estratégia de busca (Julho, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Embase<br><a href="https://www.embase.com">https://www.embase.com</a>                           | ('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<br><a href="http://lilacs.bvsalud.org/">http://lilacs.bvsalud.org/</a>                   | ("Kidney Diseases" OR Chronic Kidney Disease" OR "Kidney Insufficiency" OR "Kidney Dysfunction" OR "Renal Failure") AND ("Saliva" OR "Salivary Changes")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| LIVIVO<br><a href="https://www.livivo.de/">https://www.livivo.de/</a>                           | ((("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<br><a href="http://www.ncbi.nlm.nih.gov/pubmed">http://www.ncbi.nlm.nih.gov/pubmed</a>   | ((("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<br><a href="https://scielo.org/">https://scielo.org/</a>                                 | ("Kidney Diseases" OR Chronic Kidney Disease" OR "Kidney Insufficiency" OR "Kidney Dysfunction" OR "Renal Failure") AND ("Saliva" OR "Salivary Changes")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Scopus<br><a href="http://www.scopus.com/">http://www.scopus.com/</a>                           | ("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<br><a href="http://apps.webofknowledge.com/">http://apps.webofknowledge.com/</a> | ("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")                                                                                                                                                                                                                                                                                                               |
| OpenGrey<br><a href="http://www.opengrey.eu/">http://www.opengrey.eu/</a>                       | ("Kidney Diseases" OR Chronic Kidney Disease" OR "Kidney Insufficiency" OR "Kidney Dysfunction" OR "Renal Failure") AND ("Saliva" OR "Salivary Changes")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| OpenThesis<br><a href="http://www.openthesis.org/">http://www.openthesis.org/</a>               | ("Kidney Diseases" OR Chronic Kidney Disease" OR "Kidney Insufficiency" OR "Kidney Dysfunction" OR "Renal Failure") AND ("Saliva" OR "Salivary Changes")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

## **Seleção dos estudos**

Antes de selecionar os estudos, foi realizado um exercício de calibração, no qual os revisores discutiram os critérios de elegibilidade e os aplicaram a uma amostra de 20% dos estudos recuperados para determinar a concordância interexaminadores. Após atingir um nível adequado de concordância ( $Kappa \geq 0,81$ ), os revisores [cego] realizaram uma análise metódica dos títulos dos estudos (primeira fase) e aqueles não relacionados ao tema foram eliminados. Na segunda fase, os resumos dos estudos foram avaliados com aplicação inicial dos critérios de elegibilidade. Os títulos que atendiam aos objetivos do estudo, mas não apresentavam resumos disponíveis, foram analisados na fase seguinte. Posteriormente, na terceira fase, os estudos elegíveis tiveram seus textos completos lidos na íntegra para verificar se atendiam aos critérios de elegibilidade. Em caso de não localização dos textos completos, foi realizada comutação bibliográfica (COMUT) e contato por e-mail com o autor correspondente a fim de obtê-los. Textos completos publicados em outra língua, que não inglês ou português, foram traduzidos para aplicação dos critérios de elegibilidade. Todas as fases foram realizadas de forma independente por dois revisores e, em caso de dúvida ou discordância, um terceiro revisor [cego] foi consultado para tomar a decisão final.

## **Coleta dos dados**

Antes da extração dos dados, para garantir a consistência entre os revisores [cego] foi realizado um exercício de calibração, no qual os dados de três estudos elegíveis foram extraídos em conjunto. Um terceiro revisor [cego] conduziu a etapa de calibração.

Foram extraídas as seguintes informações dos artigos: identificação do estudo (autor, ano, país, local da pesquisa e aplicação de critérios éticos), características da amostra (número de pacientes com DRC, número de pacientes saudáveis para estudos que requerem grupo controle, estágio da DRC dos pacientes, distribuição por sexo e idade média), características da coleta e processamento (método de coleta da saliva, momento de coleta da saliva, tipo de análise salivar e tipo de análise estatística aplicada) e os resultados principais (valores da média e desvio padrão da taxa de fluxo, pH, níveis de fosfato, fósforo e cálcio salivar, principais desfechos de cada estudo). Em caso de informações incompletas ou insuficientes, o autor correspondente foi contatado por e-mail.

## Avaliação do risco de viés

Dois autores independentes [cego] avaliaram o risco de viés e a qualidade individual dos estudos elegíveis usando as Ferramentas de avaliação crítica da JBI para estudos transversais (Moola et al., 2020) e para estudos quase-experimentais (Tufanaru et al., 2020), de acordo com o respectivo desenho de estudo. Como forma de calibração, os autores analisaram um estudo elegível em conjunto, com a presença de um terceiro revisor [cego] responsável por solucionar as divergências em caso de dúvidas.

Para os estudos de desenho transversal, foram aplicadas as seguintes perguntas: Q1. Os critérios de inclusão na amostra foram claramente definidos? Q2. Os sujeitos do estudo e o ambiente foram descritos em detalhes? Q3. A exposição foi medida de forma válida e confiável? Q4. Foram usados critérios objetivos e padronizados para a medição da condição? Q5. Foram identificados fatores de confusão? Q6. Foram estabelecidas estratégias para lidar com fatores de confusão? Q7. Os resultados foram medidos de forma válida e confiável? Q8. Foi usada uma análise estatística apropriada? (Moola et al., 2020)

Já para os estudos quase-experimentais aplicaram-se as perguntas: Q1. Está claro no estudo qual é a "causa" e qual é o "efeito"? Q2. Os participantes foram incluídos em alguma comparação semelhante? Q3. Os participantes foram incluídos em alguma comparação que recebeu tratamento / cuidado semelhante, além da exposição ou intervenção de interesse? Q4. Existia um grupo controle? Q5. Houve várias medições do resultado antes e depois da intervenção / exposição? Q6. O acompanhamento foi completo e, em caso negativo, as diferenças entre os grupos em termos de acompanhamento foram adequadamente descritas e analisadas? Q7. Os resultados dos participantes foram medidos da mesma maneira? Q8. Os resultados foram medidos de forma confiável? Q9. Foi usada uma análise estatística apropriada? (Tufanaru et al., 2020).

Cada estudo foi categorizado de acordo com o percentual de respostas positivas às questões correspondentes ao instrumento de avaliação. Cada questão poderia ser respondida como: “Sim” - se o estudo não apresentasse viés quanto ao domínio avaliado pela questão; ou “Não” - se o estudo apresentou viés em relação ao domínio avaliado pela questão; ou “Incerto” - se o estudo não forneceu informações suficientes para avaliar o viés da questão; ou “Não aplicável” - se a pergunta não era adequada para o estudo. O risco de viés foi considerado **Alto** quando o estudo obteve 49% ou menos de respostas "sim", **Moderado** quando o estudo obteve 50% a 69% de respostas "sim" e **Baixo** quando o estudo atingiu 70% ou mais de "sim" (Rodrigues et al., 2020).

## Síntese dos dados e metanálise

Os dados coletados foram organizados e descritos de maneira descritiva/narrativa (síntese qualitativa) de acordo com os achados apresentados em cada um dos artigos selecionados. Além disso, foi realizada a extração das informações quantitativas apresentadas em cada estudo, as quais foram organizadas em tabelas e posteriormente importadas para o software estatístico Stata 16.1 (StataCorp LLC, College Station, TX, USA).

Para buscar responder à pergunta de pesquisa 1, foi realizada uma metanálise que comparou o valor médio de cada um dos indicadores de interesse (cálcio, fluxo, fosfato, fósforo e pH) entre pacientes que realizaram hemodiálise e indivíduos saudáveis. Com o objetivo de responder à pergunta de pesquisa 2, os valores médios dos mesmos cinco indicadores de interesse nos momentos pré e pós hemodiálise foram comparados. Embora os cinco indicadores fossem de interesse, uma metanálise só foi considerada desde que houvesse três estudos selecionados para cada indicador – caso contrário, não foi estimada uma medida combinada em virtude do limitado número de estudos.

Em ambas as perguntas, a medida de efeito calculada foi a diferença de médias padronizada. Esta medida representa a diferença, em desvios padrão, entre as amostras sendo comparadas. No caso da pergunta de pesquisa 1, a medida de efeito foi calculada diretamente através de uma metanálise para cada indicador de interesse. Já para a pergunta de pesquisa 2, considerando que as amostras comparadas não eram independentes entre si (medidas repetidas dos pacientes em dois pontos no tempo – pré e pós hemodiálise), foi estimado o valor médio combinado de cada indicador de interesse em cada ponto no tempo. Por fim, a diferença de médias padronizada entre os dois grupos foi estimada, evitando viés nas medidas de efeito calculadas (Cuijpers et al., 2016).

Todas metanálises foram conduzidas considerando efeitos aleatórios proposto por DerSimonian-Laird. Três medidas de heterogeneidade foram consideradas nas análises: i) estatística do  $I^2$ ; ii) estatística do  $\tau^2$ ; e iii) estatística do  $H^2$ . O  $I^2$  representa o percentual da variabilidade entre os estudos causada por heterogeneidade, excluindo erros de amostragem. O  $\tau^2$  representa o tamanho da variância entre os estudos, enquanto o  $H^2$  o nível de heterogeneidade entre os estudos, onde  $H^2 = 1$  representa homogeneidade. Meta regressões foram ajustadas considerando o método de coleta da saliva (estimulado ou não estimulado) e a idade média dos participantes em cada estudo para identificar possíveis moderadores. Todas as análises consideraram um nível de significância de 5%.

## **RESULTADOS**

### **Seleção dos estudos**

Na primeira fase de seleção dos estudos, foram rastreados 4574 registros, distribuídos em nove bases de dados eletrônicas, incluindo a “literatura cinzenta”. Após a remoção dos estudos duplicados, restaram 3283 registros para a análise. A leitura cuidadosa dos títulos excluiu 3078 registros. Duzentos e cinco estudos permaneceram para leitura dos resumos. Destes, 155 estudos foram excluídos após aplicação dos critérios de elegibilidade. Os 50 trabalhos restantes foram lidos na íntegra. Dezesete estudos foram excluídos e os motivos de sua exclusão foram registrados separadamente (Apêndice 1). Trinta e três estudos foram incluídos na análise qualitativa (Acosta et al., 2020; Alpdemir et al., 2018; Anuradha et al., 2015; Babaei et al., 2014; Bayraktar et al., 2002; Bayraktar et al., 2004; Bayraktar et al., 2009; Belazelkowska et al., 2014; Bots et al., 2007; Eraly et al., 2018; Gavalda et al., 1999; Hashemi et al., 2017; Honarmand et al., 2017; Kaushik et al., 2013; Khanum et al., 2017; Kho et al., 1999; Lasisi et al., 2018; Manley, 2014; Marinoski et al., 2019; Martins et al., 2006; Oyetola et al., 2015; Pham and Le, 2017; Postorino et al., 2002; Rodrigues et al., 2015; Savica et al., 2007; Seethalakshmi et al., 2014; Shetty et al., 2018; Thorman et al., 2010; Tomás et al., 2008; Tong et al., 2019; Zenuz et al., 2020; Yu et al., 2021; Teimoori et al., 2021). A Figura 1 apresenta detalhes do processo de busca, identificação, inclusão e exclusão dos estudos.

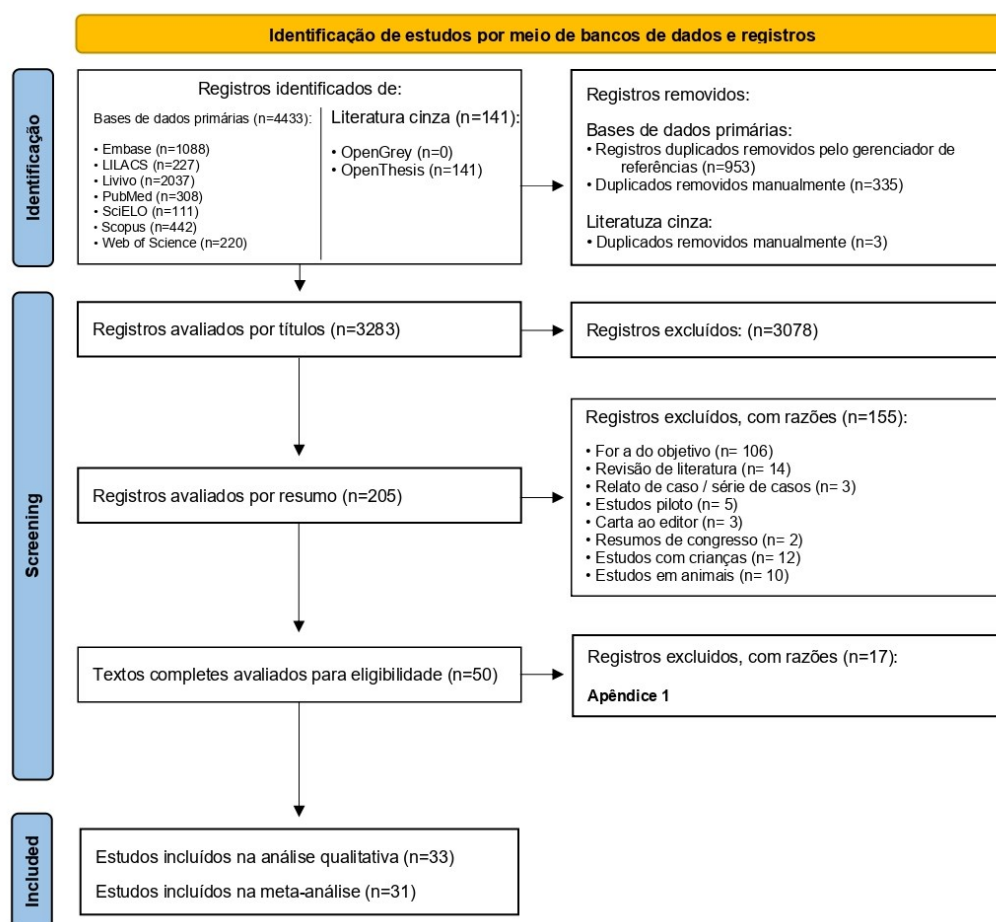


**Figura 1.** Fluxograma do processo de busca e seleção dos estudos elegíveis.

### Características dos estudos elegíveis

Os estudos foram publicados entre 1999 e 2021 e foram realizados em 17 países diferentes, com 19 estudos na Ásia (Alpdemir et al., 2018; Anuradha et al., 2015; Babae et al., 2014; Bayraktar et al., 2002; Bayraktar et al., 2004; Bayraktar et al., 2009; Eraly et al., 2018; Hashemi et al., 2017; Honarmand et al., 2017; Kaushik et al., 2013; Khanum et al., 2017; Kho et al., 1999; Pham and Le, 2017; Seethalakshmi et al., 2014; Shetty et al., 2018; Tong et al., 2019; Zenuz et al., 2020; Yu et al., 2021; Teimoori et al., 2021); 8 na Europa (Belazelkovska et al., 2014; Bots et al., 2007; Gavalda et al., 1999; Marinoski et al., 2019; Postorino et al., 2002; Savica et al., 2007; Thorman et al., 2010; Tomás et al., 2008); 3 na América do Sul (Acosta et al., 2020; Martins et al., 2006; Rodrigues et al., 2015); 2 na África (Lasisi et al., 2018; Oyetola et al., 2015) e 1 na Oceania (Manley, 2014). A amostra total incluiu 3146 participantes, sendo 1969 com DRC (casos) e 1178 considerados saudáveis (controles). A média de idade variou entre 34.7 e 69.7 anos entre os pacientes do grupo caso e entre 30.5 e 60.1 anos entre os pacientes do grupo controle.

Os homens compuseram aproximadamente 39% da amostra total entre os estudos que apresentaram dados sobre gênero.

Cinco estudos elegíveis (Belazelkovska et al, 2014; Marinoski et al., 2019; Pham and Le, 2017; Thorman et al., 2010; Tomás et al., 2008) coletaram a saliva de pacientes com DRC em estágios pré-dialíticos e dialíticos. Todos os demais estudos elegíveis apresentaram em sua amostra pacientes no estágio 5 da DRC, ou seja, pacientes já submetidos a tratamentos dialíticos, principalmente a hemodiálise. Somente três estudos (Alpdemir et al., 2018; Bayraktar et al., 2009; Thorman et al., 2010) relataram pacientes que eram submetidos à diálise peritoneal. Para a coleta da saliva, os estudos elegíveis relataram uso dos métodos não estimulado e estimulado (com diferentes artifícios de estimulação). O tempo de coleta da saliva no qual os pacientes foram submetidos variou entre um e quinze minutos ou o tempo necessário até atingir determinada quantidade de saliva, previamente estabelecida. As principais informações de cada estudo elegível estão detalhadas na Tabela 2.

**Tabela 2** – Resumo das principais características dos estudos elegíveis.

| <b>Autores, ano (país de publicação)</b> | <b>Amostra (n)</b>                                  | <b>Gênero (♀ / ♂)</b>                  | <b>Média de idade (anos) ±SD and (Variação)</b>            | <b>Estágio da DRC</b>     | <b>Parâmetros salivares</b> | <b>Metodo de coleta da saliva</b> | <b>Tipo de análise da saliva</b>                                                              | <b>Análise estatística</b>                                                  |
|------------------------------------------|-----------------------------------------------------|----------------------------------------|------------------------------------------------------------|---------------------------|-----------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Gavaldá et al., 1999 (Spain)             | Caso: 105<br>Controle: 53                           | Caso: 52♀ / 53♂<br>Controle: 24♀ / 29♂ | Caso: 58.9±14.9<br>Controle: 55.7±10.7                     | 5 (Estágio final)         | Fluxo                       | Não estimulada                    | Fluxo: Volume dividido pelo tempo                                                             | Teste t de student e Qui quadrado                                           |
| Kho et al., 1999 (South Korea)           | Caso: 22<br>Controle: 22                            | Caso: 8♀ / 14♂<br>Controle: 8♀ / 14♂   | Caso: 34.7±10.8 (18-59)<br>Controle: 30.5±7.9              | 5 (Estágio final)         | Fluxo e pH                  | Não estimulada                    | Fluxo: Volume dividido pelo tempo;<br>pH: Electrometria                                       | Teste t de student                                                          |
| Bayraktar et al., 2002 (Turkey)          | Caso: 50<br>Controle: 48                            | Caso: 27♀ / 23♂<br>Controle: 23♀ / 25♂ | Caso: 46.7±13.2 (21-69)<br>Controle: 45.7±19.1 (16-86)     | 5 (Estágio final)         | Fluxo                       | Estimulada                        | Fluxo: Volume dividido pelo tempo                                                             | Teste t de student                                                          |
| Postorino et al., 2002 (Italy)           | Caso: 63<br>Controle: 23                            | Caso: 25♀ / 38♂<br>Controle: 10♀ / 13♂ | Caso: 50.2±13.8 (13-79)<br>Controle: 46.0±13.2 (19-79)     | 5 (Estágio final)         | Fluxo                       | Estimulada                        | Fluxo: Volume dividido pelo tempo                                                             | Teste t de student e Qui quadrado                                           |
| Bayraktar et al., 2004 (Turkey)          | Caso: 72<br>Controle: 50                            | Caso: 34♀ / 38♂<br>Controle: 26♀ / 24♂ | Caso: 45.05±14.15 (18-68)<br>Controle: 43.92±18.80 (18-86) | 5 (Estágio final)         | Fluxo e pH                  | Estimulada                        | Fluxo: Volume dividido pelo tempo<br>pH: Indicador de Merck                                   | Teste t de student, Qui quadrado e correlação                               |
| Martins et al., 2006 (Brazil) *          | Caso: 15<br>Controle: 15                            | Caso: 5♀ / 10♂<br>Controle: 11♀ / 4♂   | Caso: 47.4 ± 9.73 (32-64)<br>Controle: 39.8 ± 9.97 (22-55) | 5 (Estágio final)         | Fluxo, Cálcio e Fósforo     | Estimulada                        | Fluxo: Volume dividido pelo tempo<br>Cálcio e Fósforo: Espectometria                          | ANOVA                                                                       |
| Bots et al., 2007 (Netherlands) *        | Caso: 94                                            | Caso: 30♀ / 64♂                        | Caso: 56.4±16.7 (20-85)                                    | 5 (Estágio final)         | Fluxo e pH                  | Estimulada                        | Fluxo: Volume dividido pelo tempo;<br>pH: Análise de eletrodo                                 | MANOVA                                                                      |
| Savica et al., 2007 (Italy)              | Caso: 68<br>Controle: 30                            | Caso: 29♀ / 47♂<br>Controle: 12♀ / 18♂ | Caso: 61.6±9.4<br>Controle: 52.3±6.4                       | 5 (Estágio final)         | Cálcio e Fósforo            | Não estimulada                    | Cálcio e Fósforo: Espectometria                                                               | Tesde de Kolmogorov-Smirnov; Wilcoxon-Mann-Whitney Rank                     |
| Tomás et al., 2008 (Portugal)            | Caso: 50<br>Controle: 64                            | Caso: 27♀ / 23♂<br>Controle: 34♀ / 30♂ | Caso: 64±11<br>Controle: 60±11                             | 3, 4 e 5 (<60mL/min/1.73) | Fluxo, pH e cálcio          | Não estimulada                    | Fluxo: Volume dividido pelo tempo;<br>pH e Cálcio: Colorimetria e método do eletrodo seletivo | Teste T de student; Mann-Whitney; Kolmogorov-Smirnov; Correlação de Pearson |
| Bayraktar et al., 2009 (Turkey)          | Caso: 176 (100 hemodiálise e 76 diálise peritoneal) | Caso: 44♀ / 56♂ (hemodiálise)          | Caso: 46±14 (hemodiálise) e 44±12 (diálise peritoneal)     | 5 (Estágio final)         | Fluxo e pH                  | Estimulada                        | Fluxo: Volume dividido pelo tempo;<br>pH: Indicador de Merck                                  | ANOVA One-Way, Qui                                                          |

|                                                 |                                                                                  |                                                            |                                            |                                   |                         |                             |                                                                       |                                   |
|-------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------|-----------------------------------|-------------------------|-----------------------------|-----------------------------------------------------------------------|-----------------------------------|
|                                                 | Controle: 111                                                                    | e 43♀ / 33♂<br>(diálise peritoneal)<br>Controle: 65♀ / 46♂ | Controle: 45±18                            |                                   |                         |                             |                                                                       | quadrado, Teste Kruskal–Wallis;   |
| Thorman et al., 2010 (Sweden)                   | Caso: 70 (40 pré-diálise; 21 hemodiálise e 9 diálise peritoneal)<br>Controle: 70 | Caso: § ♀ / § ♂<br>Controle: § ♀ / § ♂                     | Caso: §<br>Controle: §                     | 4 e 5                             | Fluxo                   | Não estimulada              | Fluxo: Volume dividido pelo tempo                                     | Teste T de Student                |
| Kaushik et al., 2013 (India)                    | Caso: 25<br>Controle: 25                                                         | Caso: § ♀ / § ♂<br>Controle: § ♀ / § ♂<br>r♂               | Caso: §<br>Controle: §                     | 5<br>(Estágio final)              | Fluxo e pH              | Não estimulada              | Fluxo: Volume dividido pelo tempo;<br>pH: Indicador de Merck          | Teste T de Student                |
| Babae et al., 2014 (Iran)                       | Caso: 30<br>Controle: 30                                                         | Caso: 14♀ / 16♂<br>Controle: 14♀ / 16♂                     | Caso: 51.2 (35-65)<br>Controle: (30-65)    | 5<br>(Estágio final)              | Fluxo                   | Não estimulada              | Fluxo: Volume dividido pelo tempo                                     | Mann-Whitney U; ANOVA             |
| Belazelkovska et al., 2014 (Northern Macedonia) | Caso: 60 (30 pré-diálise e 30 hemodiálise)<br>Controle: 20                       | Caso: 52♀ / 38♂<br>Controle: § ♀ / § ♂                     | Caso: 46±14<br>Controle: §                 | 4 e 5 (pré-diálise e hemodiálise) | Fluxo e pH              | Estimulada e não estimulada | Fluxo: Volume dividido pelo tempo;<br>pH: Eletrolítica                | Kruskall-Wallis-, Mann-Whitney U  |
| Manley et al., 2014 (Australia)                 | Caso: 30<br>Controle: 5                                                          | Caso: 6♀ / 24♂<br>Controle: 4♀ / 1♂                        | Caso: 69.7±14.2<br>Controle: 44.6±10.3     | 5<br>(Estágio final)              | pH, Cálcio e Fósforo    | Estimulada                  | pH: §;<br>Cálcio e Fósforo: Eletrodo específico                       | Wilcoxon                          |
| Seethalakshmi et al. 2014 (India) *             | Caso: 30                                                                         | Caso: 14♀ / 16♂                                            | Caso: 50.33                                | 5<br>(Estágio final)              | Fósforo                 | Não estimulada              | Fósforo: Colorimétrico                                                | Teste T de Student                |
| Anuradha et al., 2015 (India)                   | Caso: 50<br>Controle: 50                                                         | Caso: § ♀ / § ♂<br>Controle: § ♀ / § ♂<br>r♂               | Caso: §<br>Controle: §                     | 5<br>(Estágio final)              | Fluxo, Cálcio e Fósforo | Não estimulada              | Fluxo: Volume dividido pelo tempo;<br>Cálcio e Fósforo: Colorimétrico | Mann-Whitney U                    |
| Oyetola et al., 2015 (Nigeria)                  | Caso: 90<br>Controle: 90                                                         | Caso: § ♀ / § ♂<br>Controle: § ♀ / § ♂<br>r♂               | Caso: §<br>Controle: §                     | 5<br>(Estágio final)              | Fluxo                   | Não estimulada e estimulada | Fluxo: Volume dividido pelo tempo                                     | Teste T de Student e Qui quadrado |
| Rodrigues et al., 2016 (Brazil)                 | Caso: 60<br>Controle: 37                                                         | Caso: 31♀ / 29♂<br>Controle: 23♀ / 14♂                     | Caso: 45.6±13.5<br>Controle: 42.2±14.3     | 5<br>(Estágio final)              | Cálcio e Fósforo        | Estimulada                  | Cálcio e Fósforo: Colorimétrico                                       | Teste T de Student e Qui quadrado |
| Hashemi et al., 2017 (Iran)                     | Caso: 44<br>Controle: 44                                                         | Caso: 23♀ / 21♂<br>Controle: 23♀ / 21♂                     | Caso: 46.98±18.62<br>Controle: 46.82±18.55 | 5<br>(Estágio final)              | Calcio e Fósforo        | Estimulada                  | Cálcio e Fósforo: Colorimétrico                                       | Teste T de Student e Qui quadrado |
| Honarmand et al., 2017 (Iran)                   | Caso: 30<br>Controle: 30                                                         | Caso: § ♀ / § ♂<br>Controle: § ♀ / § ♂<br>r♂               | Caso: 38.17±16.88<br>Controle: 40.30±18.34 | 5<br>(Estágio final)              | pH e cálcio             | Não estimulada              | pH: Eletrolítico;<br>Cálcio: o-Cresolphthalein Método                 | Teste T de Student e Qui quadrado |

|                                  |                                                                                    |                                                                                    |                                                                                    |                                   |                    |                |                                                                                  |                                                                      |
|----------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------|--------------------|----------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Khanum et al., 2017 (India) *    | Caso: 30                                                                           | Caso: §                                                                            | Caso: §                                                                            | 5 (Estágio final)                 | Fluxo, pH e cálcio | Estimulada     | Fluxo: Volume dividido pelo tempo; pH: Indicador de Merck; Cálcio: Colorimétrico | Teste T de Student e Qui quadrado                                    |
| Pham and Le, 2017 (Vietnam)      | Caso: 111 (27 em estágio 3; 41 em estágio 4 e 43 em estágio 5 5) Controle: 109     | Caso: 60♀ / 51♂ Controle: 62♀ / 47♂                                                | Caso: 51.35±12.93 Controle: 48.24±18.04                                            | 3a, 3b, 4 e 5                     | Fluxo e pH         | Não estimulada | Fluxo: Volume dividido pelo tempo; pH: Eletrólito específico                     | Teste Qui Quadrado e Mann-Whitney                                    |
| Alpdemir et al., 2018 (Turkey) * | Caso: 88 (44 hemodiálise e 44 diálise peritoneal) Controle: 40                     | Caso: 14♀ / 30♂ (hemodiálise) e 18♀ / 26♂ (diálise peritoneal) Controle: 16♀ / 24♂ | Caso: 48.2±12.3 (hemodiálise) e 45.8 ±13.3 (diálise peritoneal) Controle: 43.9±8.5 | 5 (Estágio final)                 | Cálcio e Fósforo   | Não estimulada | Cálcio e Fósforo: Espectometria                                                  | Teste Kolmogorov-Smirnov, Teste T de Student; Correlação de Pearson  |
| Eraly et al., 2018 (India)       | Caso: 60 (20 <1 ano; 20 entre 1 e 3 anos e 20 >3 anos em hemodiálise) Controle: 20 | Caso: § ♀ / § ♂ Controle: § ♀ / § ♂ r♂                                             | Caso: § Controle: §                                                                | 5 (Estágio final)                 | Fluxo e pH         | Estimulada     | Fluxo: Volume dividido pelo tempo; pH: Tiras teste                               | Kruskall-Wallis; Mann-Whitney                                        |
| Lasisi et al., 2018 (Nigeria)    | Caso: 48 Controle: 50                                                              | Caso: 30♀ / 18♂ Controle: 30♀ / 20♂                                                | Caso: 39.82±11.07 Controle: 39.1±7.34                                              | 5 (Estágio final)                 | Cálcio             | Não estimulada | Cálcio: Colorimetrico                                                            | Teste T de Student e correlação de Pearson                           |
| Shetty et al., 2018 (India)      | Caso: 60 Controle: 20                                                              | Caso: § ♀ / § ♂ Controle: § ♀ / § ♂ r♂                                             | Caso: § Controle: §                                                                | 5 (Estágio final)                 | Fluxo e pH         | Estimulada     | Fluxo: Volume dividido pelo tempo; pH: kit saliva                                | Kruskal-Wallis e Mann -Whitney                                       |
| Marinoski et al., 2019 (Serbia)  | Caso: 75 Controle: 25                                                              | Caso: 19♀ / 31♂ e 7♀ / 18♂ Controle: 9♀ / 16♂                                      | Caso: 59.06 ± 14.30 (18-82) Controle: 54.20 ± 12.67 (28-80)                        | 4 e 5 (pré-diálise e hemodiálise) | Fluxo e pH         | Não estimulada | Fluxo: Volume dividido pelo tempo; pH: Tira de papel                             | Kolmogorov–Smirnov, ANOVA, Teste Qui quadrado; Correlação de Pearson |
| Tong et al., 2019 (China)        | Caso: 30 Controle: 35                                                              | Caso: 15♀ / 15♂ Controle: 20♀ / 15♂                                                | Caso: 49±13 Controle: 44±11                                                        | 5 (Estágio final)                 | pH                 | Não estimulada | pH: Indicador de Mercke                                                          | Teste T de Student, Wilcoxon, Mann-Whitney U                         |
| Acosta et al., 2020 (Venezuela)  | Caso: 12 Controle: 12                                                              | Caso: 6♀ / 6♂ Controle: 5♀ / 7♂                                                    | Caso: 48 Controle: 30                                                              | 5 (Estágio final)                 | Fluxo e Fosfato    | Não estimulada | Fluxo e Fosfato: Colorimétrico                                                   | Teste T de Student                                                   |
| Zenuz et al., 2020 (Iran) *      | Caso: 43                                                                           | Caso: 28♀ / 15♂                                                                    | Caso: 46±19 (18-77)                                                                | 5 (Estágio final)                 | Cálcio e Fósforo   | Não estimulada | Cálcio e Fósforo: Colorimétrico                                                  | Teste T de Student, Kolmogorov-Smirnov e Teste Wilcoxon              |

|                                    |                          |                                               |                                          |                         |                        |                |                                                                                   |                           |
|------------------------------------|--------------------------|-----------------------------------------------|------------------------------------------|-------------------------|------------------------|----------------|-----------------------------------------------------------------------------------|---------------------------|
| Yu et al., 2021<br>(China) *       | Caso: 100                | Caso: 66♀ / 34♂                               | Caso: 62.45±11.09<br>(34-85)             | 5<br>(Estágio<br>final) | Fluxo, pH, e<br>cálcio | Não estimulada | Fluxo: Volume dividido<br>pelo tempo;<br>pH: Tiras teste<br>Cálcio: Colorimétrico | Matriz de<br>correlação   |
| Teimoori et al.,<br>2021<br>(Iran) | Caso: 48<br>Controle: 48 | Caso: 20 ♀ / 28 ♂<br>Controle: 20 ♀ / 28<br>♂ | Caso: 53.48±1.88<br>Controle: 59.32±1.63 | 5<br>(Estágio<br>final) | Fluxo, pH, e<br>cálcio | Não estimulada | Fluxo: Volume dividido<br>pelo tempo;<br>pH: Tiras teste                          | Teste t e Qui<br>quadrado |

\* - Estudos quase-experimentais (Pré-Pós hemodiálise); § - Não reportado pelo estudo.

## Risco de viés individual dos estudos

Na análise do risco de viés dos estudos elegíveis de desenho transversal, 10 estudos (Savica et al., 2007; Tomás et al., 2008; Thorman et al., 2010; Belazelkovska et al., 2014; Manley, 2014; Oyetola et al., 2015; Rodrigues et al., 2015; Pham and Le, 2017; Lasisi et al., 2018; Tong et al., 2019) apresentaram baixo risco de viés, 15 (Gavaldá et al., 1999; Kho et al., 1999; Bayraktar et al., 2002; Postorino et al., 2002; Bayraktar et al., 2004; Bayraktar et al., 2009; Babaei et al., 2014; Kaushik et al., 2016; Hashemi et al., 2017; Honarmand et al., 2017; Eraly et al., 2018; Shetty et al., 2018; Marinoski et al., 2019; Acosta et al., 2020; Teimoori et al., 2021) apresentaram risco moderado e um estudo (Anuradha et al., 2015) apresentou alto risco de viés ou baixa qualidade metodológica. Já na análise do risco de viés dos estudos quase-experimentais, todos os estudos (Martins et al., 2006; Bots et al., 2007; Seethalakshmi et al., 2014; Khanum et al., 2017; Alpdemir et al., 2018; Zenuz et al., 2020; Yu et al., 2021) apresentaram baixo risco de viés. A Tabela 3 apresenta informações detalhadas sobre o risco de viés dos estudos elegíveis.

Apenas quatro estudos de desenho transversal tiveram resposta “Sim” às perguntas 5 e 6, indicando que a maioria dos estudos elegíveis não identificou e não estabeleceu estratégias para lidar com fatores de confundimento. Já para a pergunta 3 referente aos estudos de desenho transversal, apenas oito estudos obtiveram resposta “Sim”, demonstrando que o diagnóstico da DRC foi mencionado no estudo de maneira incerta ou não foi mencionado.

Quatro estudos quase-experimentais tiveram resposta “Não” à pergunta 4 porque não possuíam grupo controle. A pergunta 5 referente aos estudos quase-experimentais foi “Incerto” para todos os estudos porque eles não deixaram claro quantas medições pré-pós teste foram realizadas. Já a pergunta 6, relativa aos estudos quase-experimentais, foi considerada “Não aplicável” em todos os estudos elegíveis porque os pós-testes foram realizados imediatamente após hemodiálise, sem acompanhamento.

**Tabela 3** – Risco de viés avaliado pelas ferramentas de avaliação crítica da JBI (*Joanna Briggs Institute*) para estudos transversais (Moola et al., 2020) e para estudos quase-experimentais (Tufanaru et al., 2020).

| Autor, ano                  | Q.1 | Q.2 | Q.3 | Q.4 | Q.5 | Q.6 | Q.7 | Q.8 | Q.9 | % sim/ risco   |
|-----------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----------------|
| <b>Estudos transversais</b> |     |     |     |     |     |     |     |     |     |                |
| Gavaldá et al., 1999        | --  | √   | U   | √   | --  | --  | √   | √   | *   | 50/ Moderado   |
| Kho et al., 1999            | √   | √   | --  | √   | --  | --  | √   | √   | *   | 62,5/ Moderado |
| Bayraktar et al., 2002      | --  | √   | --  | √   | --  | --  | √   | √   | *   | 50/ Moderado   |
| Postorino et al., 2002      | √   | √   | --  | √   | --  | --  | √   | √   | *   | 62,5/ Moderado |
| Bayraktar et al., 2004      | --  | √   | --  | √   | --  | --  | √   | √   | *   | 50/ Moderado   |

|                                    |    |    |    |    |    |    |   |   |   |                |
|------------------------------------|----|----|----|----|----|----|---|---|---|----------------|
| Savica et al., 2007                | ✓  | ✓  | -- | ✓  | ✓  | ✓  | ✓ | ✓ | * | 87,5/ Baixo    |
| Tomás et al., 2008                 | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓ | ✓ | * | 100/ Baixo     |
| Bayraktar et al., 2009             | ✓  | ✓  | -- | ✓  | -- | -- | ✓ | ✓ | * | 62,5/ Moderado |
| Thorman et al., 2010               | ✓  | ✓  | ✓  | ✓  | -- | -- | ✓ | ✓ | * | 75/ Baixo      |
| Babae et al., 2014                 | -- | ✓  | -- | ✓  | -- | -- | ✓ | ✓ | * | 50/ Moderado   |
| Belazelkovska et al., 2014         | ✓  | ✓  | ✓  | ✓  | -- | -- | ✓ | ✓ | * | 75/ Baixo      |
| Manley, 2014                       | ✓  | ✓  | ✓  | ✓  | -- | -- | ✓ | ✓ | * | 75/ Baixo      |
| Anuradha et al., 2015              | -- | U  | U  | ✓  | -- | -- | ✓ | ✓ | * | 37,5/ Alto     |
| Oyetola et al., 2015               | ✓  | ✓  | U  | ✓  | ✓  | ✓  | ✓ | ✓ | * | 87,5/ Baixo    |
| Rodrigues et al., 2015             | ✓  | ✓  | ✓  | ✓  | -- | -- | ✓ | ✓ | * | 75/ Baixo      |
| Kaushik et al., 2016               | ✓  | ✓  | -- | ✓  | -- | -- | ✓ | ✓ | * | 62,5/ Moderado |
| Hashemi et al., 2017               | ✓  | ✓  | -- | ✓  | -- | -- | ✓ | ✓ | * | 62,5/ Moderado |
| Honarmand et al., 2017             | ✓  | ✓  | -- | ✓  | -- | -- | ✓ | ✓ | * | 62,5/ Moderado |
| Pham and Le, 2017                  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓ | ✓ | * | 100/ Baixo     |
| Eraly et al., 2018                 | ✓  | U  | -- | ✓  | -- | -- | ✓ | ✓ | * | 50/ Moderado   |
| Lasisi et al., 2018                | ✓  | ✓  | ✓  | ✓  | -- | -- | ✓ | ✓ | * | 75/ Baixo      |
| Shetty et al., 2018                | ✓  | U  | -- | ✓  | -- | -- | ✓ | ✓ | * | 50/ Moderado   |
| Marinoski et al., 2019             | ✓  | ✓  | U  | ✓  | -- | -- | ✓ | ✓ | * | 62,5/ Moderado |
| Tong et al., 2019                  | ✓  | ✓  | ✓  | ✓  | -- | -- | ✓ | ✓ | * | 75/ Baixo      |
| Acosta et al., 2020                | ✓  | ✓  | -- | ✓  | -- | -- | ✓ | ✓ | * | 62,5/ Moderado |
| Teimoori et al., 2021              | ✓  | -- | U  | ✓  | -- | -- | ✓ | ✓ | * | 50/ Moderate   |
| <b>Estudos quase-experimentais</b> |    |    |    |    |    |    |   |   |   |                |
| Martins et al., 2006               | ✓  | ✓  | ✓  | ✓  | U  | NA | ✓ | ✓ | ✓ | 77,8/ Baixo    |
| Bots et al., 2007                  | ✓  | ✓  | ✓  | -- | U  | NA | ✓ | ✓ | ✓ | 66,7/ Moderado |
| Seethalakshmi et al. 2014          | ✓  | ✓  | ✓  | -- | U  | NA | ✓ | ✓ | ✓ | 66,7/ Moderado |
| Khanum et al., 2017                | ✓  | ✓  | ✓  | -- | U  | NA | ✓ | ✓ | ✓ | 66,7/ Moderado |
| Alpdemir et al., 2018              | ✓  | ✓  | ✓  | ✓  | U  | NA | ✓ | ✓ | ✓ | 77,8/ Baixo    |
| Zenuz et al., 2020                 | ✓  | ✓  | ✓  | -- | U  | NA | ✓ | ✓ | ✓ | 66,7/ Moderado |
| Yu et al., 2021                    | ✓  | ✓  | ✓  | -- | U  | NA | ✓ | ✓ | ✓ | 75/ Low        |

✓ - sim; -- - Não; U- Incerto; NA – Não aplicável; \* - Não relacionado ao estudo.

## Resultados específicos dos estudos elegíveis

Vinte e três estudos (Acosta et al., 2020; Anuradha et al., 2015; Babae et al., 2014; Bayraktar et al., 2002; Bayraktar et al., 2004; Bayraktar et al., 2009; Belazelkovska et al., 2014; Bots et al., 2007; Eraly et al., 2018; Gavaldá et al., 1999; Kaushik et al., 2013; Khanum et al., 2017; Kho et al., 1999; Marinoski et al., 2019; Martins et al., 2006; Oyetola et al., 2015; Pham and Le, 2017; Postorino et al., 2002; Shetty et al., 2018; Thorman et al., 2010; Tomás et al., 2008; Yu et al., 2021; Teimoori et al., 2021) analisaram o fluxo salivar. Entre os estudos que analisaram a saliva coletada de pacientes DRC e controles, dezesseis (Gavaldá et al., 1999; Kho et al., 1999; Bayraktar et al., 2002; Bayraktar et al., 2004; Martins et al., 2006; Bayraktar et al., 2009; Thorman et al., 2010; Babae et al., 2014; Belazelkovska et al., 2014; Anuradha et al., 2015; Oyetola et al., 2015; Kaushik et al., 2016; Pham and Le, 2017; Eraly et al., 2018; Shetty et al., 2018; Marinoski et al., 2019; Teimoori et al., 2021) apresentaram redução significativa nos pacientes DRC quando comparados aos controles e os demais (Postorino et al., 2002;

Tomás et al., 2008; Acosta et al., 2020) não relataram diferença significativa. Todos os estudos quase-experimentais (predialise and postdialise) (Martins et al., 2006; Bots et al., 2007; Khanum et al., 2017; Yu et al., 2021) apresentaram diferença estatística significativa entre pacientes DRC antes e após a hemodiálise.

Dezessete estudos (Bayraktar et al., 2004; Bayraktar et al., 2009; Belazelkovska et al., 2014; Bots et al., 2007; Eraly et al., 2018; Honarmand et al., 2017; Kaushik et al., 2013; Khanum et al., 2017; Kho et al., 1999; Manley, 2014; Marinoski et al., 2019; Pham and Le, 2017; Shetty et al., 2018; Tomás et al., 2008; Tong et al., 2019; Teimoori et al., 2021; Yu et al., 2021) analisaram o pH salivar. O pH foi significativamente maior em doze estudos (Kho et al., 1999; Bayraktar et al., 2004; Tomás et al., 2008; Bayraktar et al., 2009; Kaushik et al., 2013; Honarmand et al., 2017; Pham and Le, 2017; Eraly et al., 2018; Shetty et al., 2018; Marinoski et al., 2019; Tong et al., 2019; Teimoori et al., 2021) na saliva coletada de pacientes DRC comparado com controles. Apenas dois estudos (Bellazelkovska et al., 2014; Manley, 2014) não apresentaram diferença significativa. Já nos estudos quase-experimentais (pré-diálise e pós-diálise), um deles (Bots et al., 2007) apresentou diferença estatística significativa e outros dois (Khanum et al., 2017; Yu et al., 2021) não observaram diferença no pH salivar antes e após a hemodiálise.

Quatorze estudos (Alpdemir et al., 2018; Anuradha et al., 2015; Hashemi et al., 2017; Honarmand et al., 2017; Khanum et al., 2017; Lasisi et al., 2018; Manley, 2014; Martins et al., 2006; Rodrigues et al., 2016; Savica et al., 2007; Tomás et al., 2008; Zenuz et al., 2020; Teimoori et al., 2021; Yu et al., 2021) analisaram a concentração de cálcio presente na saliva. Entre os estudos que analisaram a saliva coletada de portadores de DRC e controles saudáveis, sete deles (Tomás et al., 2008; Anuradha et al., 2015; Rodrigues et al., 2016; Hashemi et al., 2017; Alpdemir et al., 2018; Lasisi et al., 2018; Teimoori et al., 2021) apresentaram diferença estatisticamente significativa, sendo que dois (Tomás et al., 2008; Anuradha et al., 2015) indicaram redução da concentração de cálcio na saliva de pacientes DRC e os outros cinco estudos (Teimoori et al., 2021; Rodrigues et al., 2016; Hashemi et al., 2017; Alpdemir et al., 2018; Lasisi et al., 2018) indicaram aumento da concentração deste íon nos pacientes DRC. Outros três estudos (Martins et al., 2006; Manley, 2014; Honarmand et al., 2017) indicaram concentração de cálcio salivar similar em ambos os grupos. O estudo de Savica et al. (2007) não apresentou dados dos níveis de cálcio nos sujeitos controle, impossibilitando esta análise. Já entre os estudos quase-experimentais (predialise e postdialise), dois estudos (Alpdemir et al., 2018; Yu et al., 2021) apresentaram aumento significativo de cálcio salivar após a

hemodiálise, e outros três (Martins et al., 2006; Khanum et al., 2017; Zenuz et al., 2020) não observaram significância estatística.

Quatro estudos (Acosta et al., 2020; Alpdemir et al., 2018; Manley, 2014; Seethalakshmi et al., 2014) analisaram os níveis de fosfato salivar. Em um estudo (Alpdemir et al., 2018) que analisou a saliva coletada de pacientes DRC e controles, houve diferença estatística de maneira significativa e nos demais (Manley, 2014; Acosta et al., 2020) não foi demonstrado diferença significativa. Já entre os estudos quase-experimentais (predialysis and postdialysis), o estudo de Alpdemir et al. (2018) apresentou diferença estatisticamente significativa e o estudo de Seethalakshmi et al. (2014) indicou que este dado era similar entre controles e pacientes DRC.

Seis estudos (Anuradha et al., 2015; Hashemi et al., 2017; Martins et al., 2006; Rodrigues et al., 2016; Savica et al., 2007; Zenuz et al., 2020) analisaram os níveis de fósforo salivar. Entre os estudos que analisaram a saliva coletada de doentes e controles, cinco deles (Martins et al., 2006; Savica et al., 2007; Anuradha et al., 2015; Rodrigues et al., 2016; Hashemi et al., 2017) indicaram aumento significativo em pacientes DRC em comparação com controles. Já entre os estudos quase-experimentais (predialise and postdialise), o estudo de Martins et al. (2006) apresentou redução significativa da concentração de fósforo salivar nos pacientes DRC após uma sessão de hemodiálise em comparação com antes da hemodiálise e outro estudo (Zenuz et al., 2020) indicou similaridade nesta comparação antes e após a hemodiálise.

A Tabela 4 apresenta os resultados quantitativos e os principais desfechos dos estudos elegíveis de forma detalhada.

### **Síntese dos resultados e metanálise**

O estudo de Thorman et al. (2010) não separou dados quantitativos dos pacientes que realizavam hemodiálise ou diálise peritoneal, e o estudo de Savica et al. (2007) não apresenta dados quantitativos do grupo controle. Desta forma, apenas 31 estudos foram incluídos nas análises quantitativas (meta-análises).

Primeiramente reportamos resultados referentes à pergunta de pesquisa 1, onde pacientes e indivíduos saudáveis foram comparados. Ao todo, nove estudos compararam os valores médios de cálcio entre os grupos, demonstrando alta heterogeneidade entre os achados ( $I^2 = 96.2\%$  e  $H^2 = 26.5$ ). Não houve diferença dos valores médios de cálcio comparando indivíduos que realizaram hemodiálise com indivíduos saudáveis (SMD = 0.38; IC 95% = -0.50; 1.25;  $p = 0.400$ ) (Figura 2).

Com relação ao fluxo salivar, 20 estudos foram incluídos na análise (Figura 3). De forma similar às concentrações de cálcio, houve alta heterogeneidade entre os estudos ( $i^2 = 95.4\%$  e  $H^2 = 21.8$ ). Apesar disso, 90% dos estudos incluídos nessa análise tiveram a mesma direção de efeito – demonstrando fluxo salivar reduzido em pacientes. A medida combinada identificou que o fluxo salivar em pacientes que realizaram hemodiálise foi 1.87 desvios padrão menor (IC 95% = -2.38; -1.36;  $p < 0.001$ ) quando comparados aos indivíduos saudáveis.

A concentração de fósforo na saliva de pacientes e indivíduos saudáveis foi comparada em quatro estudos. Não foi identificada heterogeneidade entre os estudos incluídos ( $i^2 = 0.0\%$  e  $H^2 = 1.0$ ). A diferença de médias padronizada foi 0.86 desvios padrão (IC 95% = 0.63; 1.09;  $p < 0.001$ ) maior em pacientes em comparação aos indivíduos saudáveis (Figura 4).

Por fim, os níveis de pH também foram comparados em 14 estudos. A heterogeneidade entre os estudos foi considerada alta ( $i^2 = 90.7\%$  e  $H^2 = 10.7$ ), apesar disso 78.5% dos estudos incluídos demonstraram a mesma direção do efeito (maiores níveis de pH em pacientes). A medida combinada estimada pela metanálise demonstrou que o pH foi 1.47 desvios padrão maior (IC 95% = 0.98; 1.96;  $p < 0.001$ ) em comparação aos indivíduos saudáveis (Figura 5). Os níveis de fosfato não foram comparados, porque apenas dois estudos consideraram este indicador.

**Tabela 4 – Principais resultados dos estudos elegíveis.**

| Autores, ano           | Média±SD                                                                     | Diferença média (%) | Média<br>prédiálise<br>±SD  | Média<br>posdiálise ±SD      | Diferença média (%) | Principais desfechos                                                                                                                                                                                                                                                                              |
|------------------------|------------------------------------------------------------------------------|---------------------|-----------------------------|------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fluxo salivar (mL/min) |                                                                              |                     |                             |                              |                     |                                                                                                                                                                                                                                                                                                   |
| Gavaldá et al., 1999   | Caso: U, 0.26±0.28<br>S, 0.76±0.38<br>Controle: U, 0.28±0.16<br>S, 1.26±0.76 | U, 8<br>S, 65       | ¥                           | ¥                            | ¥                   | O fluxo salivar dos controlees foi significativamente maior em comparação com os doentes, para os métodos de coleta estimulada. Não foi encontrada correlação significante entre fluxo reduzido em doentes e maior formação de placa e cálculo dental.                                            |
| Kho et al., 1999       | Caso: U, 0.3±0.18<br>Controle: U, 0.45±0.25<br>Caso: S, 0.8±0.5              | U, 50               | ¥                           | ¥                            | ¥                   | A taxa de fluxo salivar em doentes mostrou-se significativamente menor em comparação aos controlees                                                                                                                                                                                               |
| Bayraktar et al., 2002 | Controle: S, 1.5±0.5                                                         | S, 88               | ¥                           | ¥                            | ¥                   | O fluxo salivar nos doentes foi significativamente menor que nos controlees, independentemente do período de terapia dialítica.                                                                                                                                                                   |
| Postorino et al., 2002 | Caso: ST, 1.65±0.66<br>Controle: ST, 2.05±0.65                               | ST, 24              | ¥                           | ¥                            | ¥                   | Os doentes apresentaram fluxo salivar reduzido em relação aos controlees e esta redução foi relacionada, em sua maioria, a alterações degenerativas nas glândulas salivares.                                                                                                                      |
| Bayraktar et al., 2004 | Caso: S, 0.69±0.31<br>Controle: S, 1.64±0.44                                 | S, 138              | ¥                           | ¥                            | ¥                   | Doentes apresentaram taxas de fluxo salivar significativamente menores em comparação com os controlees.                                                                                                                                                                                           |
| Martins et al., 2006 * | Caso: S, 0.81±0.31<br>Controle: S, 1.12±0.2                                  | S, 38               | S, 0.81±0.31                | S, 1.18±0.54                 | S, 46               | A taxa de fluxo salivar dos pacientes antes da sessão de hemodiálise foi significativamente menor em comparação com os controlees e com os pacientes após sessão de hemodiálise. Estes resultados contribuem para validar a importância da hemodiálise no controle do fluxo e composição salivar. |
| Bots et al., 2007 *    | ¥                                                                            | ¥                   | U, 0.3±0.23<br>S, 1.05±0.71 | U, 0.41±0.25<br>S, 1.23±0.74 | U, 37<br>S, 17      | Tanto nos métodos de coleta salivar não estimulado e estimulado, a taxa de fluxo salivar nos pacientes analisados foi significativamente maior após a sessão de hemodiálise em comparação com a taxa de fluxo antes da sessão.                                                                    |
| Tomás et al., 2008     | Caso: U, 0.39±0.13<br>Controle: U, 0.35±0.14                                 | U, -10              | ¥                           | ¥                            | ¥                   | A taxa de fluxo salivar não mostrou alterações significativas entre doentes em estágios moderado, severo e terminal com os controlees. A relação entre as alterações salivares detectadas e status de saúde oral ainda não foram completamente estabelecidas.                                     |
| Bayraktar et al., 2009 | Caso: S, 0.7±0.32<br>Controle: S, 1.64±0.45                                  | S, 134              | ¥                           | ¥                            | ¥                   | O fluxo salivar em pacientes saudáveis foi significativamente maior do que nos doentes em hemodiálise. Taxas diminuídas no fluxo salivar foram relacionadas a risco aumentado de cárie.                                                                                                           |

|                            |                                                                                   |                                                                                       |              |              |       |                                                                                                                                                                                                                                                                             |
|----------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------|--------------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Thorman et al., 2010       | Caso HD e PD:<br>U, 0.2±0.22<br>S, 1.3±0.73                                       | U, 50<br>S, 46                                                                        | ¥            | ¥            | ¥     | A taxa de fluxo salivar estimulada apresentou baixa significativa entre os doentes, independente da fase da DRC, quando comparada aos controlees. Já a taxa de fluxo não estimulada não mostrou alterações significativas entre os grupos de doentes e controlees.          |
| Babae et al., 2014         | Controle: U, 0.3±0.19<br>S, 1.9±1.25<br>Caso: U, 0.31± §<br>S, 0.47± §            | U, 55<br>S, 60                                                                        | ¥            | ¥            | ¥     | O fluxo salivar foi significativamente mais baixo nos doentes em comparação com os controlees em ambos os métodos de coleta da saliva. Este dado pode estar relacionado à xerostomia relatada pelos doentes.                                                                |
| Belazelkovska et al., 2014 | Controle: U, 0.48± §<br>S, 0.75± §<br>Caso: U, 0.31±0.21<br>S, 0.59±0.35          | U, 74<br>S, 222                                                                       | ¥            | ¥            | ¥     | Pacientes em hemodiálise apresentaram menores taxas significativas de fluxo salivar quando comparado aos controlees. A redução no fluxo afetou negativamente as condições orais dos pacientes, com ocorrência de manifestações orais e lesões.                              |
| Anuradha et al., 2015      | Controle: U, 0.54±0.2<br>S, 1.9±0.42<br>Caso: U, 0.41± §<br>Controle: U, 0.48± §  | U, 17                                                                                 | ¥            | ¥            | ¥     | O fluxo salivar foi significativamente menor nos doentes do que nos controlees. As manifestações orais mais comuns nos doentes foram palidez da mucosa, hipoplasia dos dentes, gosto metálico e língua fissurada.                                                           |
| Oyetola et al., 2015       | Caso: U, 0.47±0.2<br>S, 0.81±0.38<br>Controle: U, 0.76±0.45<br>S, 1.61±0.79       | U, 62<br>S, 99                                                                        | ¥            | ¥            | ¥     | Os doentes apresentaram taxas de fluxo salivar estimulada e não estimulada significativamente menores quando comparados aos controlees. A diminuição no fluxo mostrou relação significativa com efeitos orais como alterações no paladar, sensação de queimação e halitose. |
| Kaushik et al., 2016       | Caso: U, 0.31±0.01<br>S, 0.66±0.02<br>Controle: U, 0.52±0.06<br>S, 1.16±0.11      | U, 68<br>S, 76                                                                        | ¥            | ¥            | ¥     | Os pacientes apresentaram taxas de fluxo salivar significativamente menores que os controlees em ambos os métodos de coleta da saliva. Manifestações orais como mau odor e xerostomia foram verificados nos pacientes e podem ser relacionados ao fluxo salivar reduzido.   |
| Khanum et al., 2017 *      | ¥                                                                                 | ¥                                                                                     | U, 0.46±0.27 | U, 0.84±0.24 | U, 83 | A taxa de fluxo salivar dos pacientes sofreu elevação significativa após a sessão de hemodiálise. As alterações salivares mostraram influência nos achados clínicos orais.                                                                                                  |
| Pham and Le, 2017          | Caso: U, 0.11±0.02<br>Controle: U, 0.38±0.11                                      | U, 245                                                                                | ¥            | ¥            | ¥     | A taxa de fluxo salivar não estimulada foi significativamente menor em doentes quando comparado aos controlees.                                                                                                                                                             |
| Eraly et al., 2018         | Caso em HD < 1 ano:<br>S, 1.2±0.61<br>Caso em HD entre 1 - 3 anos: S,<br>0.98±0.5 | Caso em HD < 1 ano X<br>Controle: 23<br>Caso em HD entre 1 - 3<br>anos X Controle: 50 | ¥            | ¥            | ¥     | O fluxo salivar dos doentes apresentou-se menor à medida que o tempo de tratamento dialítico aumentou, sendo que os tempos de diálise entre 1-3 anos e maior que 3 anos obtiveram diferença significativa quando comparado ao grupo controlee.                              |

|                        |                                                    |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
|------------------------|----------------------------------------------------|--------------------------------------------------------|--------------------------|--------------------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                        | Caso em HD > 3 anos:<br>S, 0.89±0.45               | Caso em HD > 3 anos X<br>Controle: 65                  |                          |                          |                |                                                                                                                                                                                                                                                   |
|                        | Controle: S, 1.47±0.52                             |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
|                        | Caso em HD < 3 meses:<br>S, 1.31±0.34              | Caso em HD < 3 meses<br>X Controle: 40                 |                          |                          |                |                                                                                                                                                                                                                                                   |
| Shetty et al., 2018    | Caso em HD entre 6 meses - 2<br>anos: S, 0.99±0.32 | Caso em HD entre 6<br>meses - 2 anos X<br>Controle: 86 | ¥                        | ¥                        | ¥              | Todos os grupos de pacientes em hemodiálise<br>apresentaram taxas de fluxo salivar significativamente<br>menores em comparação com os controlees, sendo que<br>este fluxo se apresentou mais baixo nos grupos com<br>maior tempo sob hemodiálise. |
|                        | Caso em HD > 2 anos:<br>S, 0.73±0.26               | Caso em HD > 2 anos X<br>Controle: 152                 |                          |                          |                |                                                                                                                                                                                                                                                   |
|                        | Controle: S, 1.84±0.34                             |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
| Marinoski et al., 2019 | Caso: U, 0.3±0.16                                  | U, 70                                                  | ¥                        | ¥                        | ¥              | A taxa de fluxo salivar de doentes, independente do<br>grupo, foi significativamente menor que a taxa de<br>fluxo salivar dos controlees.                                                                                                         |
|                        | Controle: U, 0.51±0.19                             |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
| Acosta et al., 2020    | Caso: U, 0.69± §                                   | U, 28                                                  | ¥                        | ¥                        | ¥              | Pacientes com DRC apresentaram fluxo salivar<br>reduzido em relação aos controlees.                                                                                                                                                               |
|                        | Controle: U, 0.88± §                               |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
| Yu et al., 2021        | ¥                                                  | ¥                                                      | U, 0.15±0.1              | U, 0.19±0.12             | U, 27          | O fluxo salivar aumentou após a hemodiálise                                                                                                                                                                                                       |
|                        | Caso: U, 0.23±0.08                                 |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
| Teimoori et al., 2021  | Controle: U, 0.34±0.13                             | U, 48                                                  | ¥                        | ¥                        | ¥              | Pacientes com DRC apresentou fluxo salivar menor do<br>que pacientes saudáveis                                                                                                                                                                    |
| <b>pH salivar</b>      |                                                    |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
|                        | Caso: U, 7.51±0.44                                 |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
| Kho et al., 1999       | Controle: U, 6.62±0.22                             | U, -12                                                 | ¥                        | ¥                        | ¥              | O pH foi significativamente mais elevado nos doentes.<br>Pacientes apresentaram alterações orais como odor<br>urêmico, boca seca e mudanças no paladar que podem<br>estar relacionados às alterações salivares.                                   |
|                        |                                                    |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
|                        | Caso: S, 8.15±0.72                                 |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
| Bayraktar et al., 2004 | Controle: S, 7.16±0.75                             | S, -12                                                 | ¥                        | ¥                        | ¥              | Os doentes apresentaram níveis de pH<br>significativamente maiores que os controlees. Não foi<br>identificada relação entre alterações no fluxo e pH<br>salivar com resultados negativos no índice CPOD nos<br>pacientes.                         |
|                        |                                                    |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
|                        | ¥                                                  | ¥                                                      | U, 7.2±0.6<br>S, 7.3±0.5 | U, 6.7±0.5<br>S, 6.9±0.9 | U, -7<br>S, -5 | O pH dos pacientes sofreu redução significativa após a<br>sessão de hemodiálise. Estes resultados contribuem<br>para afirmar que a hemodiálise gera efeitos agudos na<br>saliva dos pacientes em tratamento.                                      |
|                        |                                                    |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
|                        | Caso: U, 7.71±1.18                                 |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
| Tomás et al., 2008     | Controle: U, 6.79±0.77                             | U, -12                                                 | ¥                        | ¥                        | ¥              | O pH apresentou-se significativamente elevado em<br>doentes quando comparado aos controlees. A relação<br>entre as alterações salivares detectadas e status de<br>saúde oral ainda não foram completamente<br>estabelecidas.                      |
|                        |                                                    |                                                        |                          |                          |                |                                                                                                                                                                                                                                                   |
| Bayraktar et al., 2009 | Caso: S, 8.12±0.32                                 | S, -12                                                 | ¥                        | ¥                        | ¥              | O pH mostrou ser significativamente mais elevado nos<br>doentes do que no grupo controlee.                                                                                                                                                        |

|                            |                                                                             |                                                   |             |             |      |                                                                                                                                                                                                          |
|----------------------------|-----------------------------------------------------------------------------|---------------------------------------------------|-------------|-------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kaushik et al., 2013       | Controle: S, 7.16±0.76<br>Caso: U, 7.24±0.25<br>S, 7.28±0.25                | U, -9<br>S, -1                                    | ¥           | ¥           | ¥    | O pH dos pacientes foi significativamente mais alto em relação aos controlees somente no método de coleta não estimulada.                                                                                |
|                            | Controle: U, 6.6±0.32<br>S, 7.24±0.25<br>Caso: U, 7.26±0.35<br>S, 6.91±0.35 |                                                   |             |             |      |                                                                                                                                                                                                          |
| Belazelkovska et al., 2014 | Controle: U, 7.34±0.05<br>S, 6.78±0.32<br>Caso: S, 6.98±0.24                | U, 1<br>S, -2                                     | ¥           | ¥           | ¥    | As alterações no pH não foram significativas para ambos os métodos de coleta da saliva entre doentes e controlees.                                                                                       |
|                            | Controle: S, 6.72±0.21<br>Caso: U, 8.41±0.76                                |                                                   |             |             |      |                                                                                                                                                                                                          |
| Manley, 2014               | Controle: S, 6.72±0.21<br>Caso: U, 8.41±0.76                                | S, -4                                             | ¥           | ¥           | ¥    | O pH não demonstrou alterações significativas entre doentes e controlees.                                                                                                                                |
| Honarmand et al., 2017     | Controle: U, 7.01±0.31                                                      | U, -17                                            | ¥           | ¥           | ¥    | O pH salivar dos doentes foi significativamente maior em relação ao pH salivar do grupo controlee.                                                                                                       |
| Khanum et al., 2017 *      | ¥                                                                           | ¥                                                 | U, 6.39±1.1 | U, 6.54±0.6 | U, 2 | O pH não sofreu alterações significativas nas análises antes e após hemodiálise. As alterações salivares mostraram influência nos achados clínicos orais.                                                |
| Pham and Le, 2017          | Caso: U, 7.8± §<br>Controle: 7.0± §                                         | U, -10                                            | ¥           | ¥           | ¥    | O pH salivar dos doentes foi significativamente maior em comparação com o grupo controlee.                                                                                                               |
|                            | Caso em HD < 1 ano: S, 6.84±0.45                                            |                                                   |             |             |      |                                                                                                                                                                                                          |
| Eraly et al., 2018         | Caso em HD entre 1 - 3 anos: S, 6.99±0.42                                   | Caso em HD < 1 ano X Controle: -3                 | ¥           | ¥           | ¥    | O pH salivar dos doentes aumentou à medida que o tempo de tratamento dialítico aumentou, sendo que todos os grupos de doentes apresentaram diferença significativa quando comparados ao grupo controlee. |
|                            | Caso em HD > 3 anos: S, 7.21±0.26                                           | Caso em HD entre 1 - 3 anos X Controle: -5        |             |             |      |                                                                                                                                                                                                          |
|                            | Controle: S, 6.65±0.27<br>Caso em HD < 3 meses: S, 6.38±0.32                | Caso em HD > 3 anos X Controle: -8                |             |             |      |                                                                                                                                                                                                          |
|                            | Caso em HD entre 6 meses - 2 anos: S, 6.75±0.35                             | Caso em HD < 3 meses X Controle: -6               |             |             |      |                                                                                                                                                                                                          |
| Shetty et al., 2018        | Caso em HD > 2 anos: S, 7.33±0.35                                           | Caso em HD entre 6 meses - 2 anos X Controle: -11 | ¥           | ¥           | ¥    | O pH foi significativamente maior entre os doentes, aumentando de acordo com tempos maiores de hemodiálise.                                                                                              |
|                            | Controle: S, 6.02±0.27<br>Caso: U, 6.88±0.22                                | Caso em HD > 2 anos X Controle: -18               |             |             |      |                                                                                                                                                                                                          |
|                            | Controle: U, 6.52±0.49                                                      |                                                   |             |             |      |                                                                                                                                                                                                          |
| Marinoski et al., 2019     | Controle: U, 6.52±0.49                                                      | U, -5                                             | ¥           | ¥           | ¥    | O pH salivar dos doentes apresentou-se significativamente maior que nos controlees.                                                                                                                      |

|                                    |                                                |        |              |              |        |                                                                                                                                                                                                                          |
|------------------------------------|------------------------------------------------|--------|--------------|--------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tong et al., 2019                  | Caso: U, 8.2±0.44<br>Controle: U, 7.5±0.37     | U, -9  | ¥            | ¥            | ¥      | Pacientes com DRC apresentaram pH significativamente mais elevado em relação aos controlees.                                                                                                                             |
| Yu et al., 2021                    | ¥                                              | ¥      | U, 7.83±0.75 | U, 7.3±0.83  | U, -7  | O pH da saliva foi significativamente menor após a hemodiálise                                                                                                                                                           |
| Teimoori et al., 2021              | Caso: U, 7.74± 0.29<br>Controle: U, 6.61±0.20  | U, -15 | ¥            | ¥            | ¥      | Pacientes com doença renal crônica apresentaram pH salivar significativamente maior do que os voluntários saudáveis                                                                                                      |
| Níveis salivares de cálcio (mg/dL) |                                                |        |              |              |        |                                                                                                                                                                                                                          |
| Martins et al., 2006 *             | Caso: S, 1.72±0.7<br>Controle: S, 1.42±0.62    | S, -17 | S, 1.72±0.7  | S, 1.5±0.48  | S, -13 | Os níveis de cálcio não apresentaram alterações significativas entre os grupos.                                                                                                                                          |
| Savica et al., 2007                | Caso: U, 7.21± §<br>Controle: §                | ¥      | ¥            | ¥            | ¥      | Não foram apresentados dados dos níveis de cálcio salivar do grupo controlee.                                                                                                                                            |
| Tomás et al., 2008                 | Caso: U, 2.64±2.84<br>Controle: U, 7.12±5.92   | U, 170 | ¥            | ¥            | ¥      | Os níveis de cálcio salivar foram significativamente menores em doentes do que nos controlees. A relação entre as alterações salivares detectadas e status de saúde oral ainda não foram completamente estabelecidas.    |
| Manley, 2014                       | Caso: S, 12.12±1.72<br>Controle: S, 12.92±0.28 | S, 7   | ¥            | ¥            | ¥      | Os níveis de cálcio não apresentaram alterações significativas entre doentes e controlees. Entretanto, os níveis de cálcio salivar apresentaram relação significativa com sintomas de boca seca relatados pelos doentes. |
| Anuradha et al., 2015              | Caso: U, 4.31±4.65<br>Controle: U, 6.5±2.3     | U, 51  | ¥            | ¥            | ¥      | Os níveis de cálcio foram significativamente mais altos no controlee que nos doentes.                                                                                                                                    |
| Rodrigues et al., 2016             | Caso: S, 5.36±2.31<br>Controle: S, 1.87±1.37   | S, -65 | ¥            | ¥            | ¥      | Os níveis de cálcio da saliva dos doentes foram significativamente maiores quando comparados aos níveis dos controlees.                                                                                                  |
| Hashemi et al., 2017               | Caso: S, 6.42±1.99<br>Controle: S, 2.92±1.28   | S, -55 | ¥            | ¥            | ¥      | Os níveis salivares de cálcio foram significativamente maiores nos doentes em comparação com os controlees, dessa forma, podem ser potenciais biomarcadores não invasivos de diagnóstico.                                |
| Honarmand et al., 2017             | Caso: U, 2.23±1.15<br>Controle: U, 2.47±1.33   | U, 11  | ¥            | ¥            | ¥      | Os níveis de cálcio salivar nos doentes foram menores em comparação com o grupo controlee, entretanto essa diferença não foi significativa.                                                                              |
| Khanum et al., 2017 *              | ¥                                              | ¥      | U, 8.77±0.53 | U, 8.76±0.52 | U, 0   | Os níveis de cálcio salivar não sofreram alterações significativas nas análises antes e após hemodiálise.                                                                                                                |
| Alpdemir et al., 2018 *            | Caso: U, 1.52±1.68<br>Controle: U, 3.32±2.2    | U, 118 | U, 1.52±1.68 | U, 2.93±2.36 | U, 93  | Os níveis de cálcio salivar foram significativamente mais baixos nos doentes em comparação com os controlees, mas o valor tendeu a subir após a sessão de hemodiálise.                                                   |
| Lasisi et al., 2018                | Caso: U, 6.82±3.23                             | U, -71 | ¥            | ¥            | ¥      | Os níveis de cálcio nos pacientes com DRC foram significativamente maiores do que nos controlees.                                                                                                                        |

|                                            |                                                |        |              |               |        |                                                                                                                                                                                                                                                                    |
|--------------------------------------------|------------------------------------------------|--------|--------------|---------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                            | Controle: U, 1.68±1.09                         |        |              |               |        | Altos níveis de cálcio nos doentes sugerem seu papel na baixa prevalência de cáries em pacientes com DRC.                                                                                                                                                          |
| Zenuz et al., 2020 *                       | ¥                                              | ¥      | U, 6.35±5.29 | U, 5.68±2.49  | U, -11 | Os níveis de cálcio salivar em pacientes com DRC foram menores após a sessão de hemodiálise, mas os valores de queda não foram estatisticamente significantes.                                                                                                     |
| Yu et al., 2021 *                          | ¥                                              | ¥      | U, 8.32±6.92 | U, 11.0±8.04  | U, 155 | Os níveis de cálcio na saliva foram significativamente mais altos após a hemodiálise                                                                                                                                                                               |
| Teimoori et al., 2021                      | Caso: U, 3.17±3.22<br>Controle: U, 1.77±1.41   | U, -44 | ¥            | ¥             | ¥      | Os níveis de cálcio em pacientes com DRC foi significativamente mais alto do que nos controles                                                                                                                                                                     |
| <b>Níveis salivares de fosfato (mg/dL)</b> |                                                |        |              |               |        |                                                                                                                                                                                                                                                                    |
| Manley, 2014                               | Caso: S, 30.74±3.75<br>Controle: S, 21.16±4.83 | S, -31 | ¥            | ¥             | ¥      | Os níveis de fosfato não apresentaram alterações significativas entre doentes e controlees. Entretanto, os níveis de fosfato salivar apresentaram relação significativa com sintomas de boca seca relatados pelos doentes.                                         |
| Seethalakshmi et al., 2014 *               | ¥                                              | ¥      | U, 21.1±7.99 | U, 19.09±7.61 | U, -10 | Os níveis salivares de fosfato em pacientes com DRC foram mais altos antes da sessão de hemodiálise quando comparado aos níveis após a sessão de hemodiálise.                                                                                                      |
| Alpdemir et al., 2018 *                    | Caso: U, 5.51±1.64<br>Controle: U, 3.65±0.62   | U, -34 | U, 5.51±1.64 | U, 2.66±0.9   | U, -52 | Os níveis de fosfato salivar se apresentaram significativamente mais elevado nos doentes antes da sessão de hemodiálise e tendeu a se normalizar após o tratamento.                                                                                                |
| Acosta et al., 2020                        | Caso: U, 3.19± §<br>Controle: U, 2.57± §       | U, -19 | ¥            | ¥             | ¥      | Os níveis de fosfato foram aumentados nos doentes devido retenção do íon no organismo pela doença, mas não de forma significativa. Este fato pode estar relacionado a maiores índices de cálculo dentário.                                                         |
| <b>Níveis salivares de fósforo (mg/dL)</b> |                                                |        |              |               |        |                                                                                                                                                                                                                                                                    |
| Martins et al., 2006 *                     | Caso: S, 3.04±1.57<br>Controle: S, 1.83±0.64   | S, -40 | S, 3.04±1.57 | S, 1.83±0.64  | S, -40 | Os níveis de fósforo salivar nos doentes antes da hemodiálise foram significativamente maiores que nos controlees e nos doentes após hemodiálise. Estes resultados contribuem para validar a importância da hemodiálise no controle do fluxo e composição salivar. |
| Savica et al., 2007                        | Caso: U, 30.27± §<br>Controle: U, 12.1± §      | U, -60 | ¥            | ¥             | ¥      | O nível de fósforo salivar em pacientes com DRC foi significativamente maior quando comparado aos controlees.                                                                                                                                                      |
| Anuradha et al., 2015                      | Caso: U, 9.26±4.25<br>Controle: U, 5.6±3.7     | U, -40 | ¥            | ¥             | ¥      | Os níveis de fósforo foram significativamente mais altos nos doentes quando comparados aos níveis no grupo controlee.                                                                                                                                              |
| Rodrigues et al., 2016                     | Caso: S, 18.36±7.58                            | S, -24 | ¥            | ¥             | ¥      | Os níveis de fósforo da saliva dos doentes foram significativamente maiores quando comparados aos                                                                                                                                                                  |

|                      |                                              |        |              |              |        |                                                                                                                                                                                            |
|----------------------|----------------------------------------------|--------|--------------|--------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | Controle: S, 13.96±4.21                      |        |              |              |        | níveis dos controlees. Condições secundárias, como hipotireoidismo, pareceram estar associadas às concentrações elevadas de fósforo salivar.                                               |
| Hashemi et al., 2017 | Caso: S, 5.55±1.38<br>Controle: S, 4.49±0.68 | S, -19 | ¥            | ¥            | ¥      | Os níveis salivares de fósforo foram significativamente maiores nos doentes em comparação com os controlees, dessa forma, podem ser potenciais biomarcadores não invasivos de diagnóstico. |
| Zenuz et al., 2020 * | ¥                                            | ¥      | U, 31.1±17.8 | U, 27.7±16.3 | U, -11 | Os níveis de fósforo salivar em pacientes com DRC foram menores após a sessão de hemodiálise, mas os valores de queda não foram estatisticamente significantes.                            |

\* - Estudos quase-experimentais (pré –

pós hemodiálise); ¥ - Não aplicável ao estudo; § - Não relatado; U – Saliva não estimulada; S – Saliva estimulada; ST - teste Saxon

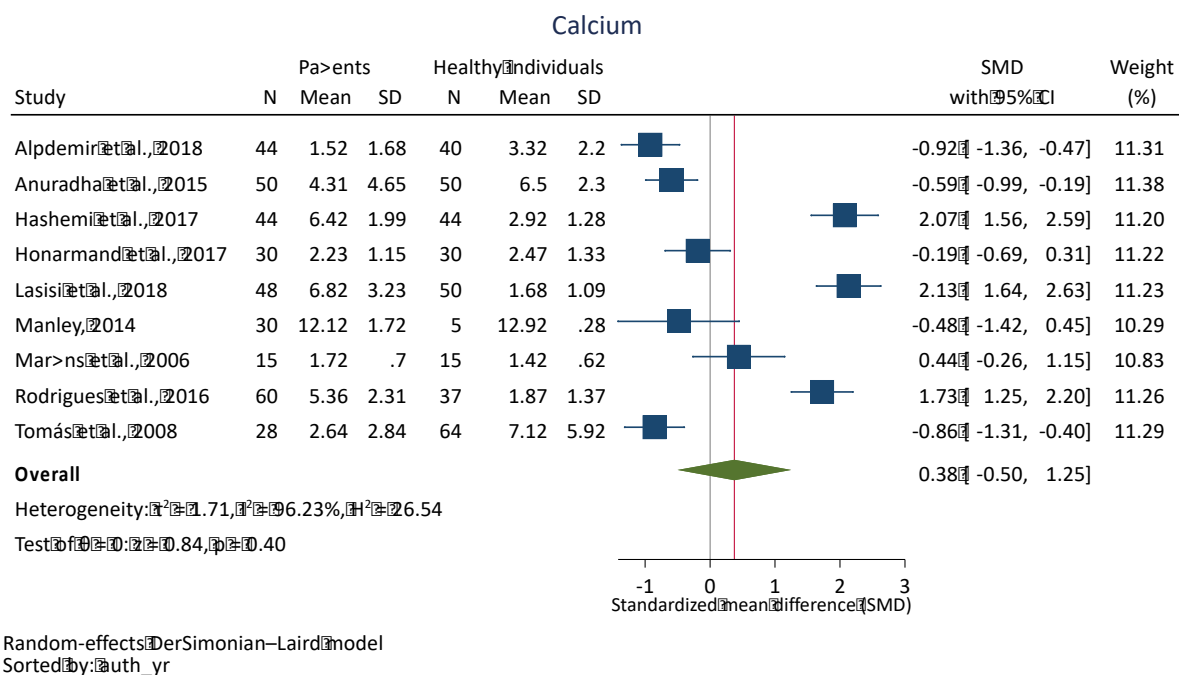


**Figura 2.** Metanálise dos níveis de concentração de cálcio entre pacientes que realizaram hemodiálise e indivíduos saudáveis.

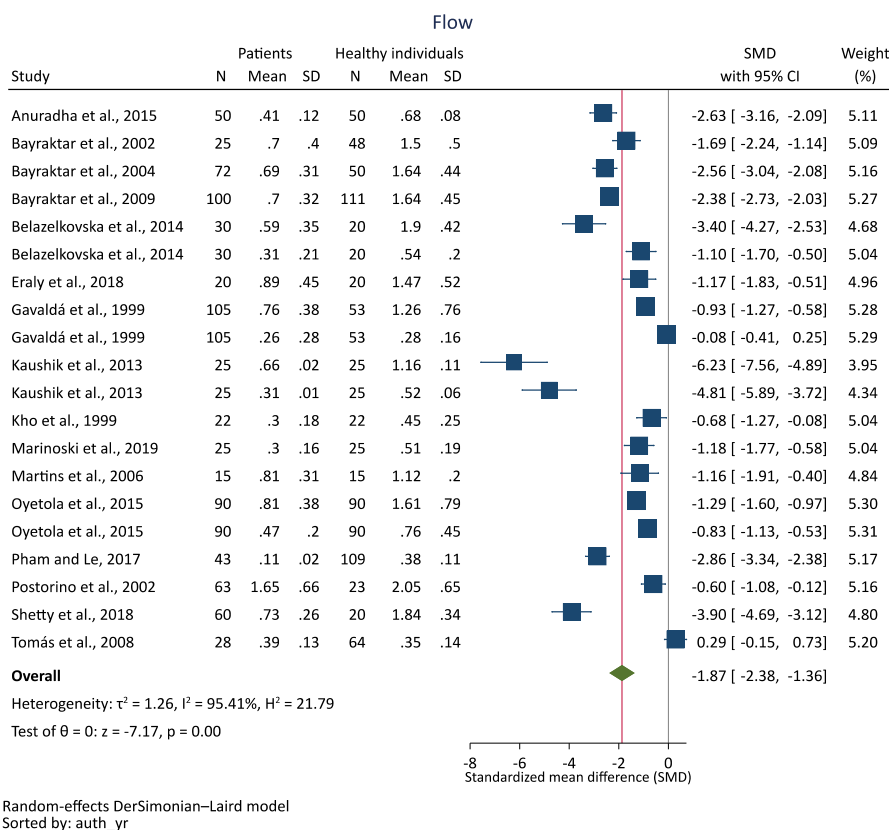
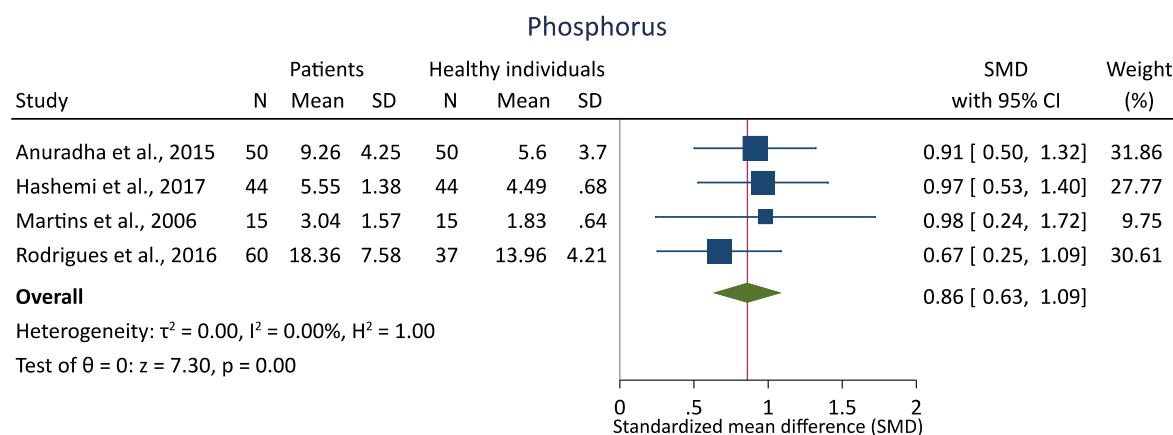
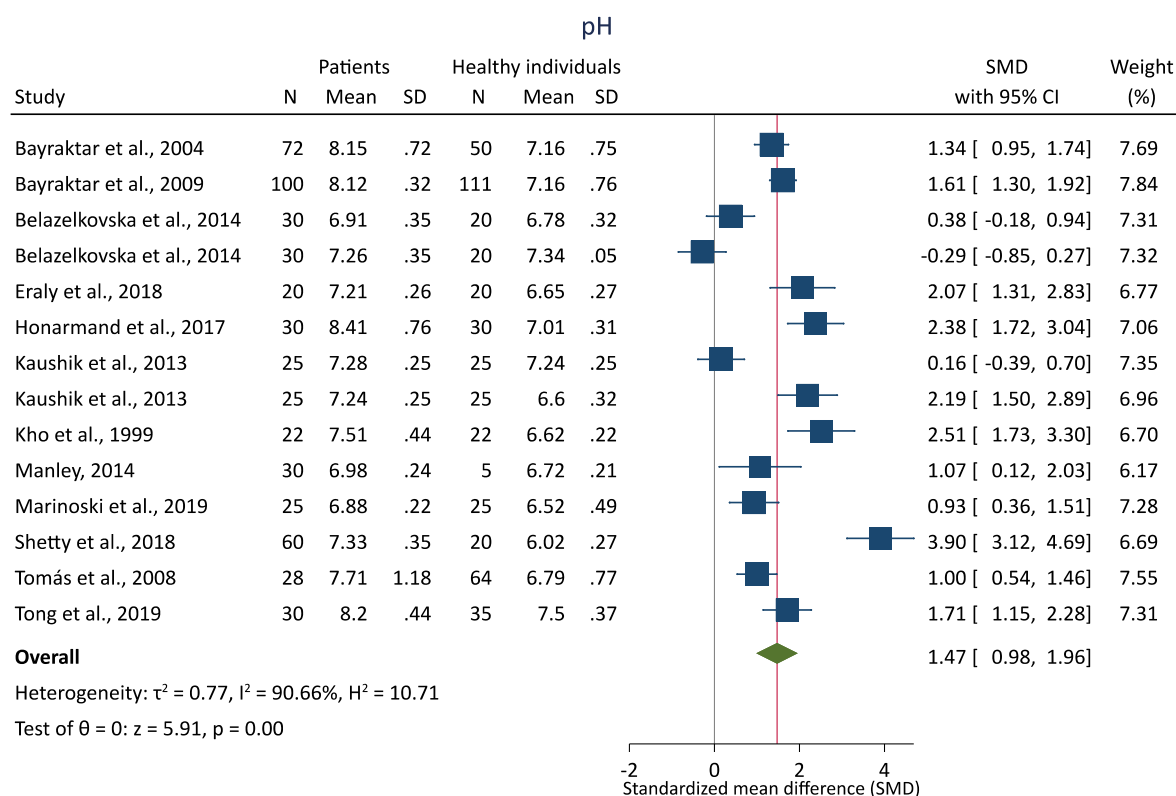


**Figura 3.** Metanálise do fluxo salivar entre pacientes que realizaram hemodiálise e indivíduos saudáveis.



Random-effects DerSimonian–Laird model  
 Sorted by: auth\_yr

**Figura 4.** Metanálise dos níveis de concentração de fósforo entre pacientes que realizaram hemodiálise e indivíduos saudáveis.



Random-effects DerSimonian–Laird model  
 Sorted by: auth\_yr

**Figura 5.** Metanálise dos níveis de concentração de pH entre pacientes que realizaram hemodiálise e indivíduos saudáveis.

Para responder à pergunta de pesquisa 2, os valores médios dos cinco indicadores nos pontos pré e pós hemodiálise foram comparados (Tabela 5). Os níveis de cálcio e pH

foram similares antes e após a hemodiálise. Em contrapartida, o fluxo salivar foi 0.61 desvios padrão menor (IC 95% = -1.00; -0.23) após a realização da hemodiálise.

**Tabela 5.** Médias agrupadas e diferença de médias padronizadas após metanálise dos níveis de concentração de cálcio, pH e fluxo salivar em dois pontos no tempo: pré e pós hemodiálise.

| <b>Indicador</b>           | <b>Pré hemodiálise</b>            | <b>Pós hemodiálise</b>            | <b>Diferença média</b>                   |
|----------------------------|-----------------------------------|-----------------------------------|------------------------------------------|
|                            | <b>Média agrupada<br/>(IC95%)</b> | <b>Média agrupada<br/>(IC95%)</b> | <b>padronizada agrupada<br/>(IC 95%)</b> |
| <b>Cálcio<sub>4</sub></b>  | 4.58 (-0.69; 9.23)                | 4.72 (0.16; 9.29)                 | 0.07 (-0.40; 0.53)                       |
| <b>Fluxo<sub>4</sub></b>   | 0.65 (0.33; 0.97)                 | 0.91 (0.48; 1.34)                 | 0.61 (0.23; 1.00)                        |
| <b>Fosfato<sub>2</sub></b> | <sub>a</sub>                      | <sub>a</sub>                      | <sub>a</sub>                             |
| <b>Fósforo<sub>2</sub></b> | <sub>a</sub>                      | <sub>a</sub>                      | <sub>a</sub>                             |
| <b>pH<sub>3</sub></b>      | 7.05 (6.77; 7.34)                 | 6.72 (6.55; 7.14)                 | -0.46 (-0.98; 0.05)                      |

a Número de estudos insuficiente para estimar medidas agrupadas (dois estudos ou menos). Números subscritos indicam a quantidade de estudos considerada em cada análise.

## DISCUSSÃO

Por meio desta meta-análise foi investigado se pacientes com doença renal crônica sob terapia de hemodiálise apresentam alterações na composição iônica, fluxo salivar e pH salivar em comparação com sujeitos saudáveis. Adicionalmente, foi avaliada a capacidade de uma sessão de hemodiálise em reverter estes parâmetros. Por meio das meta-análises foi observado que pacientes DRC apresentam redução no fluxo salivar, aumento no pH salivar e aumento da concentração de fosfato salivar, entretanto, apenas o fluxo salivar foi revertido após uma sessão de hemodiálise.

A manutenção do fluxo salivar adequado é importante na prevenção de algumas doenças orais, como cárie e doença periodontal, uma vez que o baixo fluxo salivar está relacionado à manutenção de placas e biofilmes bacterianos na cavidade oral (Hirotomi et al., 2006; Mizutani et al., 2014; Iwasaki et al., 2016). Por meio dos estudos elegíveis desta revisão e dos resultados da meta-análise, observou-se uma redução significativa no fluxo salivar de pacientes com DRC. Esse achado pode estar relacionado com algumas manifestações orais frequentemente encontradas em pacientes DRC, como a xerostomia, alteração no paladar e mucosa pálida (Anuradha et al., 2015; Hornamand et al., 2017; Marinoski et al., 2019), embora tal associação não esteja bem elucidada na literatura (Bots

et al., 2007; Hornamand et al., 2017; Marinoski et al., 2019). A redução do fluxo salivar na DRC pode estar relacionada com alterações moleculares em glândulas salivares, por medicamentos utilizadas pelos pacientes DRC (Bayraktar et al., 2004) ou por uma redução do volume de líquido extracelular nas glândulas salivares relacionado ao seu estado de hidratação e equilíbrio hidroeletrolítico (Tomás et al., 2008), entretanto, estes fenômenos não estão claramente estabelecidos.

Adicionalmente, os resultados da meta-análise também evidenciaram que uma sessão de hemodiálise é capaz de aumentar o fluxo salivar dos pacientes DRC, como esperado, revertendo as alterações estabelecidas com a DRC. Uma hipótese para esse achado é o mecanismo de ultra filtração renal promovido pelo procedimento de hemodiálise, causando um aumento de volume intravascular, levando assim a uma maior perfusão das glândulas e, conseqüentemente, maior produção de saliva (Yu et al., 2021). Considerando que a hemodiálise pode restabelecer as concentrações dos íons sódio, potássio, bicarbonato, creatinina e ureia para valores mais próximos ao nível fisiológico (Hemodialysis Adequacy 2006 Work Group, 2006), sugere-se que o restabelecimento do equilíbrio hidroeletrolítico esteja relacionado com o aumento da secreção salivar após uma sessão de hemodiálise. Sabe-se que aumentos de pressão arterial estão associados com aumento da atividade simpática dirigida para as glândulas salivares, o que promove aumento da vasoconstrição glandular e pode reduzir o fluxo salivar (Sabino-Silva et al., 2012). Desta forma, a redução de pressão arterial é frequente na maioria dos pacientes hipertensos que realizam hemodiálise (Landry & Oliver, 2006) e pode estar relacionada com o restabelecimento da atividade simpática para as glândulas salivares e da secreção salivar após uma sessão de hemodiálise. Esse achado enfatiza a importância da hemodiálise não apenas à níveis de filtração de moléculas tóxicas, mas também à melhora na saúde oral dos indivíduos com DRC (Khanum et al., 2017; Yu et al., 2021).

O pH da saliva foi outra importante propriedade investigada em diversos estudos elegíveis. Os resultados da meta-análise demonstraram que o pH salivar se apresenta elevado em pacientes DRC em relação aos sujeitos saudáveis; tal achado pode ser justificado pelo fato de pacientes com DRC apresentarem níveis elevados de ureia na composição salivar (Bagalad et al., 2017; Alpademir et al., 2018), a qual é metabolizada pela microbiota oral em dióxido de carbono e amônia (Chen et al., 2016), o que eleva o pH salivar (Honarmand et al., 2017). Neste contexto, considerando que um pH ácido favorece o processo de desmineralização da estrutura dental (Seethalakshmi et al., 2016), isto pode estar correlacionado com menor prevalência de cárie em pacientes DRC embora

o fluxo salivar também esteja frequentemente reduzido (Andrade et al., 2014). Uma vez que um pH salivar baixo fornece um ambiente acidogênico para o crescimento de bactérias acidúricas que levam à cárie dental (Seethalakshmi et al., 2016), dessa forma, um pH elevado pode funcionar como um fator de proteção à desmineralização do esmalte.

Embora a hemodiálise pode reduzir as concentrações de ureia na saliva (Rodrigues et al., 2021), os resultados da nossa meta-análise demonstraram que este fator isolado não foi suficiente para redução do pH salivar imediatamente após a hemodiálise. Esse resultado pode ser justificado pelo fato de os estudos que realizaram a coleta de saliva imediatamente após os procedimentos de diálise, o que pode ser um tempo curto para avaliar as mudanças no metabolismo da ureia em mecanismos intracelulares de células acinosas de glândula salivar e consequente redução do pH salivar. Estudos futuros devem ser realizados para observar a influência da hemodiálise no pH salivar em intervalos maiores após a sessão de hemodiálise.

Os níveis de cálcio salivar também é outro importante biomarcador em pacientes com DRC. Acredita-se que concentrações mais altas de cálcio na saliva possam funcionar como um fator de proteção para o desenvolvimento de cárie, porém como um fator de risco para a formação de cálculo (Fiyaz et al., 2013; Dogan et al., 2016). Apesar de alguns estudos elegíveis desta revisão destacarem a associação de pacientes com DRC possuírem maiores chances de apresentarem cálculo dental (Gavaldá et al., 1999; Kaushik et al., 2013; Honarmand et al., 2017; Acosta et al., 2020), não há evidências consistentes que comprovem essa associação e não foi o objetivo da presente revisão. Além disso, os resultados da nossa meta-análise não observaram alterações significativas nos níveis de cálcio de pacientes de DRC quando comparados a pacientes saudáveis, apesar da alta inconsistência encontrada nos resultados individuais dos estudos. Acredita-se que não há uma metodologia padronizada pelos estudos, que utilizaram diferentes métodos laboratoriais para calcular os níveis de cálcio na saliva, além de diferenças da própria população, impedindo de estabelecer conclusões mais enfáticas sobre essa variável.

Assim como o cálcio, os níveis de fósforo e fosfato salivares são importantes biomarcadores que podem sofrer influência pela doença renal crônica, sendo inclusive descritos como possíveis formas de avaliar a necessidade de hemodiálise (Rodrigues et al., 2016). Esta meta-análise evidenciou aumento nos níveis de fósforo salivar em pacientes DRC em comparação com sujeitos saudáveis, o que pode ser justificado pelas alterações patofisiológicas dos rins, que promovem aumento deste componente no plasma e na saliva (Kim et al., 2014).

Destacamos que os resultados destas meta-análises devem ser interpretados com cautela devido à alta heterogeneidade das análises e que não puderam ser explicadas por análises de meta-regressão, o que pode ser justificado pelas diferentes populações, metodologias empregadas na avaliação dessa variável e nas características clínicas dos pacientes que não puderam ser avaliadas individualmente, como comorbidades associadas à DRC, tempo de hemodiálise, faixa etária e uso de medicamentos.

Por outro lado, pelo nosso conhecimento, esta revisão sistemática da literatura é pioneira ao investigar as alterações salivares de pacientes DRC, bem como, ao avaliar os efeitos da hemodiálise na saliva. Além disso, uma extensa busca na literatura, sem restrições de ano ou idioma de publicação garantiram que o máximo de estudos publicados fossem incluídos.

Do ponto de vista clínico odontológico, essa revisão sistemática chama atenção para alterações salivares importantes e que devem ser levadas em consideração no momento de planejamento dos casos de pacientes com falência renal, como por exemplo tratamento da xerostomia e alterações do paladar causada pela redução do fluxo salivar, monitoramento da condição periodontal e de aparecimento de lesões orais, com objetivo de reduzir o impacto dessas manifestações orais na qualidade de vida do paciente.

## **CONCLUSÃO**

É possível concluir que pacientes com doença renal crônica apresentam alterações importantes nas propriedades e composição salivares, como redução de fluxo e aumento do pH, além de maiores níveis de fósforo, porém sem diferença nos níveis de cálcio e fosfato quando comparados à voluntários saudáveis. Observou-se também que a hemodiálise é capaz de aumentar o fluxo salivar desses pacientes. Esses achados podem auxiliar no entendimento das manifestações orais presentes em pacientes com doença renal crônica e na conscientização de necessidade de planejamentos clínicos individualizados durante o tratamento odontológico desse grupo de pacientes.

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**Apêndice 1** – Estudos excluídos durante a fase de leitura de textos completos (n=17).

| <b>Study excluded</b>       | <b>Reason for exclusion</b>                       |
|-----------------------------|---------------------------------------------------|
| Holmes et al., 1960         | Sem grupo controle                                |
| Epstein et al., 1980        | Não foi feita coleta da saliva como um todo       |
| Coroneo et al., 1981        | Não localizado                                    |
| Earbaum and Quinton, 1981   | Não foi feita coleta da saliva como um todo       |
| Van der Lichte et al., 1983 | Não localizado                                    |
| Kao et al., 2000            | Não foi feita coleta da saliva como um todo       |
| Mydlik et al., 2006         | Não localizado                                    |
| Bots et al., 2007           | Sem grupo controle                                |
| Espitia Nieto et al., 2007  | Sem grupo controle                                |
| Jach et al., 2007           | Não localizado                                    |
| Vesterinen et al., 2007     | Sem grupo controle                                |
| Savica et al., 2008         | Sobreposição de amostra com outro estudo elegível |
| Vidyullatha et al., 2010    | Sem grupo controle                                |
| Fregoneze et al., 2013      | Pacientes pediátricos incluídos                   |
| Yajamanam et al., 2016      | Pacientes com doença renal aguda                  |
| Nylund et al., 2017         | Sem grupo controle                                |
| Kumar et al., 2020          | Grupo controle com pacientes com outras doenças   |

**Apêndice 1 - Referências**

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# Conclusões

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#### 4 – CONCLUSÕES

- A avaliação da creatinina e ureia salivar parecem adequadas para diagnosticar a doença renal crônica em pacientes nos estágios três, quatro ou cinco. Assim, os pacientes com doença renal crônica poderiam se beneficiar clinicamente na substituição do sangue pela saliva como material biológico usado nas análises da função renal em estágios específicos de atendimento ao paciente.
- Há correlação entre os níveis de ureia e creatinina salivar e sanguínea após a hemodiálise, uma vez que ambas as moléculas apresentaram redução significativa após o procedimento em ambos os fluidos. Tal resultado indica que a saliva pode ser utilizada como forma de acompanhamento dos níveis de uréia e creatinina entre sessões de hemodiálise.
- Pacientes com doença renal crônica apresentam alterações importantes nas propriedades e composição salivares, como redução de fluxo e aumento do pH, além de maiores níveis de fósforo, porém sem diferença nos níveis de cálcio e fosfato quando comparados à voluntários saudáveis. Observou-se também que a hemodiálise é capaz de aumentar o fluxo salivar desses pacientes. Desse modo, pacientes com falência renal exigem planejamentos clínicos odontológicos individualizados, com o objetivo de minimizar os impactos orais causados pela doença.

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# Anexos

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## **6. ANEXOS**

### **6.1 Normas dos periódicos**

A) Clinical Oral Investigations

<https://www.springer.com/journal/784/submission-guidelines>

B) Brazilian Oral Research

<https://www.scielo.br/revistas/bor/iinstruc.htm>

C) Archives of Oral Biology

<https://www.elsevier.com/journals/archives-of-oral-biology/0003-9969/guide-for-authors>