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Salivary protein in patients with Chronic Kidney Disease-associated to periodontal and peri-implant disease: Systematic review

Dissertation presented to the Universidade Católica Portuguesa

toobtainthemaster'sdegreeinD ental Medicine

By:

Lisandra Taísa Reginaldo Tavares

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"Adoramosaperfeição,porquenãoa podemos ter; repugná-la-íamos se a tivéssemos. O perfeito é o desumano porque o humano é imperfeito."

Livro do desassossego, Bernardo Soares (Fernando Pessoa)

To my mother and father that support me unconditionally and made this possible.

To my brother whom I love despite all the disagreements.

To my grandmother Lourdes, who would be so proud, but Alzheimer's took that opportunity away from us.

To my grandparents, Alcina and Adolfo that I love so much.

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The final year is perhaps the most difficult and rewarding year of academic life, it is a year of many emotions and work. The present year, 2020, has been more difficult than expected, we lost celebrations, skipped interships and had to adapt to a new reality. However, despite all the individual effort and dedication, I did not walk this path alone. Therefore, I would like to thank all those who provided and are still providing me with the best possible final course.

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Resumo

Introdução: A periodontite é a doença inflamatória mais prevalente no mundo. Vários autores propõem que a inflamação periodontal difunde-se sistematicamente, sendo associada á doença cardiovascular, sendo esta a causa de morte mais frequente em pacientes com doença renal crónica (CKD). Os biomarcadores salivares têm um grande potencial no diagnóstico e na correlação de ambas as doenças, podem também ser importantes na monitorização da inflamação sistémica.

Objetivo: Desta forma, o objetivo deste estudo é analisar a associação entre a doença renal crônica e a periodontite / periimplantite, analisando biomarcadores salivares.

Materiais e métodos: Realizou-se uma pesquisa eletrónica sistemática nas bases de dados PubMed (MEDLINE), EMBASE e Web of Science, esta foi conduzida por três revisores independentes de forma a identificar estudos clínicos realizados em seres humanos publicados entre janeiro de 2009 e janeiro de 2020, sem restrições geográficas ou de idioma. Esta revisão sistemática seguiu as diretrizes do PRISMA. A presente revisão sistemática foi registada no PROSPERO.

Resultados: A estratégia de pesquisa identificou 7051 artigos, mas apenas um atendeu a todos os critérios de inclusão e exclusão. O artigo incluído estudou 4 biomarcadores salivares, sTrem-1, PYGLRP1, IL-1βeMMP -8 em pacientes na fase pré-diálise com *follow-u*p de 157 meses. Os resultados do estudo, por meio de uma análise de fatores de confusão, mostraram que a periodontite teve uma influência significativa no aumento dos valores desses biomarcadores inflamatórios.

Conclusão: Não é possível estabelecer uma relação direta de causa-efeito entre a periodontite e a doença renal crónica, mas este trabalho conclui que um efeito correlacionando através dos biomarcadores pró-inflamatórios analisados pode ser causado. Mais estudos controlados são sugeridos para reforçar essa conclusão fraca.

Palavras chave: periodontite, peri-implantite, doença renal crónica, biomarcadores salivares, revisão sistemática.

Abstract

Background: Periodontitis is the most prevalent inflammatory disease worldwide. Different authors have proposed that periodontal inflammation spreads systemically being associated with cardiovascular disease, the most frequent death cause in chronic kidney disease patients. Salivary biomarkers have a big potential in the diagnosis and correlation of both diseases, it can also be important in monitoring the systemic inflammation.

Aim: Therefore, the aim of this study is to analyse the association between chronic kidney disease and periodontitis / periimplantitis by analysing salivary biomarkers.

Materials and methods: A systematic electronic search through PubMed (MEDLINE), EMBASE and Web of Science databases was conducted by three independent reviewers to identify clinical studies performed in humans and published between January 2009 and January 2020, with no geographical or language restrictions. This systematic review followed the PRISMA guidelines. The present systematic review was registered in the PROSPERO.

Results: Search strategy identified 7051 protentional eligible articles but only one met all the inclusion and exclusion criteria. The included article studied 4 salivary biomarkers, sTrem-1, PYGLRP1, IL-1β and MMP-8 in patients at predialysis stage with a follow-up of 157 months. Study results, by a confounders analysis, showed that periodontitis had a significant influence increasing the values of these inflammatory biomarkers.

Conclusion: A direct cause-effect association between periodontitis and CKD cannot be established, but this work concludes that there was an effect correlating them through the analysed proinflammatory biomarkers. More controlled studies are suggested to reinforce this weak conclusion.

Keywords: periodontitis; periimplantitis; chronic kidney disease; salivary biomarkers, systematic review.

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Introduction

Chronic kidney disease (CKD) consists in a progressive and irreversible change to the normal kidney function and/or damage to the renal parenchyma at the glomerular, tubular or endocrine level.(1–5) It is characterized by the loss of filtration capacity of the kidneys and the consequent accumulation of organic residues (urea) that cause immunodeficiency due to the increase of toxic substances in the bloodstream. In addition to this, there is a loss of hormonal production capacity, control of the electrolyte balance and blood pressure.(1–7) There are some factors associated with this disease, the main ones being obesity, diabetes mellitus, hypertensive nephrosclerosis, glomerular chronic nephritis and hypertension.

This disease is classified according to the glomerular filtration rate (GFR), stage 1: kidney damage with normal or increased GFR (> 90 m ml / min / 1.73 m2); stage 2: slight reduction in GFR (60-89 ml / min / 1.73 m2); stage 3: moderate reduction in GFR (30-59 ml / min / 1.73 m2); stage 4: marked reduction in GFR (15-29mL / min / 1.73 m2); stage 5: Renal failure (GFR <15 ml / min / 1.73 m2 or dialysis). (3,4) Patients in stage 5, that is, patients with chronic end-stage renal disease (ESRD), need substantial renal therapies such as dialysis (haemodialysis or peritoneal dialysis) or kidney transplantation. (4,5,7)

Dialysis is the treatment aimed at improving the systemic symptoms caused by the accumulation of toxic substances simulating the physiological process of glomerular filtration. Haemodialysis and peritoneal dialysis are two equally effective types of dialysis. In haemodialysis an equipment that filters the patient's blood is used to filter it of impurities and, next, to return it to the patient. In a different way peritoneal dialysis is performed through an equipment that drains a solution directly from the patient's abdomen without direct contact with his blood and is performed on an outpatient basis.(2,8)

CKD patients present oral manifestations of the disease. These occur most often in mucous and glandular tissues, supporting tissues and in dental pieces. Radiographic changes in bone density and the accumulation of dental plaque is common among these patients.(2,7) The most common symptom in dialysis patients is the pallor of mucous and glandular involvement seen in the intraoral examination due to anaemia (reduced erythropoietin synthesis). (9,10) In this group of patients, bleeding is common in addition to the effect of haemodialysis, which predisposes

patients to ecchymosis, petechiae and haemorrhages in the oral mucosa, associated with changes in platelet aggregation and renal anaemia.(9,10) Usually patients are discouraged from drinking excess fluids, so they are prone to dry mouth and retrograde parotitis. (10,11) Also related to xerostomia, one third of the haemodialysis patientshaveacharacteristichalitosis,called“uremicfetor”,andametallicflavourdue to the high content of urea in saliva and its degradation in ammonia.(2,7,12,13) In addition, the patient may also have dysgeusia, that is, when the perception of the sweet flavours and acids are altered, this being justified by the high levels of urea in the saliva and also due to the presence of dimethyl and trimethylamines. Burning mouth syndrome is frequently seen as an additional symptom in dialysis patients.(12,13) Another oral manifestation in this group is uremic stomatitis, which is a non-prevalent oral complication of unknown aetiology.(2,7) Lesions consist of localized or generalized erythematous areas, covered by pseudo-membranous exudates, which can be removed, leaving an intact or ulcerated mucosa. (12,13) Studies report that 4% of patients on haemodialysis suffer from angular cheilitis and lichen planus, which can arise in association with antihypertensive medication. (12,14)

Saliva is an acidic bio-fluid, composed of 99% water, 0.3% proteins and 0.2% organic and inorganic substances.(15) Daily, a patient secretes between 0.5L and 1.5L of saliva through the major and minor salivary glands. This biofluid is collected in a non-invasive way, which reduces the patient's anxiety levels, since there is no need for needles which makes it easier and faster to collect.(16,17) In terms of storage, this is also easier than blood as it does not clot. (17–19)

Through saliva we can diagnose various diseases related, not only to the oral cavity, but also related to psychological and systemic health through the various biomarkers that can be detected. Medicine and dentistry are two of the areas in which diagnosis through saliva is relevant. It can be applied in the respective sub-areas of these large research groups, such as nephrology and periodontal disease (periodontitis and periimplantitis).(17–23)

Over the years the tools that aid clinical diagnosis have evolved. In order to identify a pathology, a good clinical history and a clinical examination sustained by auxiliary diagnostic tests are essential. Classically, CKD is evidenced in blood and urine laboratory tests. Through the glomerular filtration rate (GFR), the presence of

CKD is evident if the rate is less than 60 ml / min / 1.73m2 for a period of three months or more. In addition to this exam, there are other types of indicators of this disease that can be researched in salivary biomarkers.(24,25) Biomarkers exist in a variety of different forms inserted in 5 different sciences of salivary diagnosis, including genomics, transcriptomics, proteomics, interatomics and metabolomics. Changes in the concentration, structure, function or action of the various components can be associated with the onset, progression or even regression of a disorder. In this way, salivary biomarkers serve as a valuable and attractive tool in the detection, risk assessment, diagnosis, prognosis and monitoring of the disease.(11,20,26)

At the salivary level, patients with chronic renal failure when compared to healthy individuals have an elevated salivary pH, an increased systemic inflammatory activity, higher concentrations of C-reactive protein (CRP), urea, sodium and potassium in contrast to the calcium values that are significantly lower.(11,27–31) Researchers have shown that the concentrations of some metabolites in saliva, such as creatinine, urea and potassium, differ according to the degree of renal failure and treatment with dialysis.(2,32) CKD patients suffer from suppression of humoral and cellular immune responses, which leads to subnormal immunoglobulin A (IgA) and immunoglobulin G (IgG) concentrations. (30) According to studies, we can also find the following altered salivary inflammatory biomarkers in patients with CKD: interleukin 1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor α (TNF-α), interferon γ (INF-γ), monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1(sICAM-1).(17)

D. Pallos et al., conducted a study on salivary changes in 3 different groups (Group: healthy/control, CKD and haemodialysis (HD) and demonstrated that there are significantly higher levels of inflammatory metabolites. Relating the values of IgA and IgG, these were found to be higher in the group of haemodialysis patients with comparatively chronic renal failure, with no significance in the comparison between healthy versus chronic renal failure. The control group showed lower levels of nitrous oxide compared to the CKD and HD groups, without differing between the CKD and HD groups. The pH was higher in the CKD group compared to the HD and control groups.(29)

Periodontal disease is one of the most prevalent chronic diseases, being characterized by an inflammatory and immunological response of periodontal tissues (supporting tissues, cementum alveolar bone and periodontal ligament), produced in response to the accumulation of a biofilm rich in Gram negative bacteria, like A*ggregatibacter actinomycetemcomitans, Prevotella intermedia, Campylobacter rectus, P. gengivalis and Capnocytophaga sp*.(2,20,33–35) Despite bacterial infection there are some risk factors, biological and behavioural, that influence the evolution of periodontitis, such as tobacco, stress, socioeconomic status, traumatic occlusion, and autoimmune diseases such as diabetes.(33,34) Periodontal disease is classified according to the new classification launched in 2018 in the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Condition and conditions.(36) According to the most recent classification, the patient can be inserted in three groups:

1. Periodontal health, conditions and gum disease:
    a. Periodontal and gingival health;
    b. Biofilm-induced gingivitis;
    c. Gingival diseases not induced by biofilm;
2. Periodontitis:
    a. Necrotizing periodontal diseases;
    b. Periodontitis;
    c. Periodontitis with manifestations of systemic diseases;
3. Other conditions that affect the periodontium.

Periodontitis can be classified by stage and degree, stages being defined from I to IV and degree from A to C. Stage I is present when we have an interproximal insertion loss (NIC) of 1-2mm, probing depth (PD) up to 4mm, with a horizontal pattern of bone resorption and without tooth loss due to periodontitis, in stage II we find a NIC between 3-4mm, PD up to 5mm with a horizontal bone resorption pattern and without tooth loss due to periodontitis, stage III patients have a NIC of 5mm or more, PS of 6mm or more, a vertical bone resorption pattern, lesions of grade II or III furcation and a loss of less than 4 teeth due to periodontitis, as for stage IV it only differs from stage III in terms of the number of teeth lost by periodontitis, 5 or more teeth, if the patient has masticatory

dysfunction, a serious defect of the bony ridge or less than 10 pairs of antagonistic teeth.(36)

Regarding the degree, periodontitis can be classified as grade A in which there is a slow progression, with a loss of up to 0.25mm per year and without risk factors (tobacco or diabetes), in grade B patients have a moderate progression between 0.25mm and 1mm per year, risk factors may be present but in which the patient smokes less than 10 cigarettes a day and has an HbA1c of less than 7%. On the other hand we will be facing a grade C when periodontitis progresses rapidly, more than 1mm per year, or if risk factors are present such as the patient being a smoker of more than 10 cigarettes per day or having HbA1c greater than 7%.(36)

At the peri implant level, clinical health is evident through the absence of clinical signs of inflammation, bleeding and/or suppuration after probing, we must compare radiographic exams and note that there were no changes in bone loss in addition to the loss observed after the physiological remodelling phase. In cases of bleeding and/or suppuration, increased probing depth and presence of bone loss, we are dealing with a case of peri-implantitis.(36)

In periodontal disease, as in the various chronic systemic diseases, early diagnosis is very important. Methods of clinical and radiographic analysis are usually used, but the analysis of fluids in the oral cavity can provide significant conclusions regarding the progression of the disease. The literature presents as hypotheses the analysis of crevicular and salivary fluid in the detection of periodontitis/periimplantitis. Saliva is the bio fluid most studied and analysed by the scientific community since it is considered like a mirror or reflection of happens in our body.(18,37)

The evolution of periodontal disease depends on the immune response of each individual. The infection generates a host defense response through neutrophils, fibroblasts, epithelial cells and monocytes, that in turn will lead to the production of prostaglandins, followed by cytokines such as IL-1, IL-6 and TNF-α that lead to resorption of the alveolar bone and consequent loss of insertion, these can be detected in the salivary analysis.(3,17,20,33,34,38,39) Other important salivary biomarkers that are increased in cases of periodontal disease have also been studied, such as metalloproteinase-8 (MMP-8), metalloproteinase-9 (MMP-9), and the inflammatory protein of macrophages-1α(MIP -1αorCCL3). (39,40) A fact to be taken

into account is that Ig-β and IL-6 produced in response to infection are increased in patients with chronic periodontal disease and are associated with decreased kidney function. (3) Studies indicate that the inflammatory response can spread systemically, which justifies the high relationship between systemic diseases and periodontal disease, such as lung diseases, diabetes and cardiovascular diseases such as atherosclerotic complications, one of the main causes of mortality in CKD.(2,3,31,33,34,41,42)

Therefore, periodontal disease and CKD have a positive correlation viability due to systemic inflammatory burden and low immunity. CKD patients may have a greater predisposition or worsening of periodontal disease or periodontal disease may be one of the aggravating factors of progression or mortality in patients with CKD. (2,3,7,17,25,31,34)

Periodontal therapy involves the elimination of dental biofilm and all factors that lead to its accumulation through chemical or mechanical means. The main objective is to promote reattachment, decrease of oral bacterial load and consequent reduction of inflammation. Thus, it can be considered that CKD and periodontal disease have a bidirectional cause-effect relationship since the presence simultaneously worsens the prognosis, due to the increased systemic inflammatory load and bacterial translocation, but the treatment and control of these can act as an adjunct therapy for both. (2,3)

According to the Kramer *et al.* (2019), at the year of 2016 data of 32 countries was collected. 687 084 patients were doing renal replacement therapy, this is a prevalence of 823 pmp.(43) Over the years, Portugal and Spain appear to be the countries were the incidence of renal replacement therapy (RRT) is higher. (43) According to the data obtained, men and patients aged over 65 years are the most affected patients and diabetes was the most frequent cause of renal disease. (43) Patients undergoing RRT modalities had a survival rate of 50.5%, therefore we are facing a high mortality rate, this becomes a serious public health problem and we have to consider all the factors that can aggravate this condition.(43) Studies indicate that periodontal disease, the most prevalent inflammatory disease worldwide, has a possible relationship with CKD, therefore, studies in this area of interest are important (2,3,7,17,25,34)

With the evolution of science and medicine, more investigations are being conducted in short periods of time. This evolution and growth increase the need for synthesis methods that allow the clinician to be aware of the different advances without wasting hours in exhaustive research. For this reason, several research matrices and data collection have been developed in order to develop transparent systematic reviews with the minimum bias.(44–48) Within this context, this systematic review seeks to analyze the correlation between CKD and periodontal disease, taking into account the protein changes in saliva through salivary biomarkers.

Justification

Systematic review and meta-analysis are essential tools used in the synthesis and compilation of primary studies in a transparent, accurate and reliable way in order to facilitate the acquisition of new knowledge, clinical based on scientific evidence, by clinicians.(44–50)

Therefore, systematic reviews with quality are important resources considering the accelerated growth of scientific information. Systematic reviews are research articles with high scientific evidence at a hierarchical level, carried out using pre-defined and explicit systematic methods, in a way that they can be reproduced. This type of study has the purpose to systematically combine the knowledge of published and unpublished studies in order to facilitate the development of projects for future research or simply for the acquisition of more up-to-date knowledge. It aims to answer a clear question, it must be exhaustive and with a defined search strategy, this must be carried out by at least two researchers in order to ensure compliance with the established criteria for inclusion and exclusion of articles. It is a careful extraction of data through the selected quality literature, in order to guarantee the maximum quality of the study. Bibliography must be restricted to scientific weight studies, evaluating the quality of the articles. (44–50)

Therefore, rigorous research planning is necessary, there are several guidelines that must be followed for the construction of an accurate systematic review.

Materials and methods

This systematic review followed the *Preferred Reporting Items for Systematic reviews and Meta-Analysis* (PRISMA) guidelines. The research was carried out based on Boolean terms. The protocol for this systematic review was registered in PROSPERO platform (Centre for Reviews and Dissemination / CRD – University of York) and, consequently, accepted with the acceptance number CRD42020168324.

Focus question

This study aimed to analyse the association between chronic kidney disease and periodontitis / periimplantitis by analysing salivary biomarkers. Based on this, the focus of this search is the analysis of salivary proteins in chronic kidney patients associated with periodontitis/ periimplantitis.

Information sources and search strategy

A systematic search of the literature published in the last ten years was carried out (1st of January 2009 – 31st of January 2020). To conduct a search as exhaustive as possible, three bibliographic databases were used, *Pubmed, Web of Science* and *Embase*. To each search engine our search was adaptad to its characteristics, based on Boolean operators (AND, OR) to combine searches, mesh terms, emtree terms and common terms. At *Pubmed, Web of Science* e *Embase* the following terms were used: Chronic Kidney Disease AND Periodontitis OR “periodontal disease” OR periimplantitis AND Inflammatory biomarkers OR Salivary biomarkers. Articles written in any language between the years of 2009 and 2020 were included. Searches in the reference lists of the included studies (cross-referencing) were also conducted. All used articles were stored in the bibliographic management platform Mendley.

Inclusion criteria

Inclusion and exclusion criteria were designed in a way that could be explicit so that any researcher or reader, following these criteria, can make the same selection of articles as the one carried out by the researchers.

Only human studies were included, articles from different languages and with less than 12 years of publication were analyzed in order to get the most recent evidence as possible.

Exclusion criteria

Previously performed systematic reviews and meta-analyses were excluded, so that pre-existing bias would not be introduced. Furthermore, studies unrelated to patients with CKD, periodontitis / periimplantitis and that do not address salivary biomarkers were excluded. Those that did not involve humans and that only analysed crevicular fluid were also excluded.

Studies selection

Regarding the selection of studies, this was carried out based on strict selection criteria, date of publication and target population. In order to be clear and replicable, the studies selection followed the inclusion and exclusion criteria detailed in table 1.

Duplicate articles were excluded, the remain were elected through the initial reading of the title and abstract. The reviewers (LTRT and SMSRPS) had no contact or discussion during the selection of the studies and any disagreements between reviewers was discussed with a third reviewer (GVOF) and he made the tiebreaker.

Data extraction and assessment of bias

It was included trials that enrolled patients with CKD and periodontitis analysing salivary biomarkers. The following data were extracted by two reviewers: year of publication, journal, language, country, objective, study design, participants (population setting), patients exclusion criteria, ethical committee, methods, study period, summary characteristics of study participants (age, gender, periodontal disease, CKD stage, HbA1c, smoking habits), saliva collection (stimulated or unstimulated), biomarkers analysed, and study results.

The Risk of Bias (RoB) was evaluated using the PROBAST methodology (Prediction model Risk Of Bias Assessment Tool), which was organized following 4 domains: participants, predictors, outcome, and analysis, which contain a total of 20 signalling questions to judge of ROB, focusing a transparent approach.

Table 1. Inclusion and exclusion criteria

Inclusion and exclusion criteria	
Inclusion	Exclusion
Clinical Study; Clinical Trial; Clinical Trial Protocol; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Research study Randomized Controlled Trial; Controlled Clinical Trial; Published in the last 10 years; Humans; Any language;	Systematic review; Review; No biomarkers analyzed; Blood biomarkers; Crevicular fluid biomarkers; Patients without CKD; Patient without periodontitis/ periimplantitis; Urinary biomarkers Animal study;

Results

Study selection

Three electronic databases were used to search for articles on the topic, a total of 7051 articles were identified through database searching, 467 on Pubmed, 4221 on Web of science and 2363 on Embase. From those, 108 were excluded due to being duplicated. Therefore, 6943 articles were screened by title and abstract based on the inclusion and exclusion criteria (Table 1). After the screening, 33 articles were included for further analysis. Subsequently, only one study met the inclusion criteria to be included in the current review, Nylund *et al.,* (2017). (Figure 1)

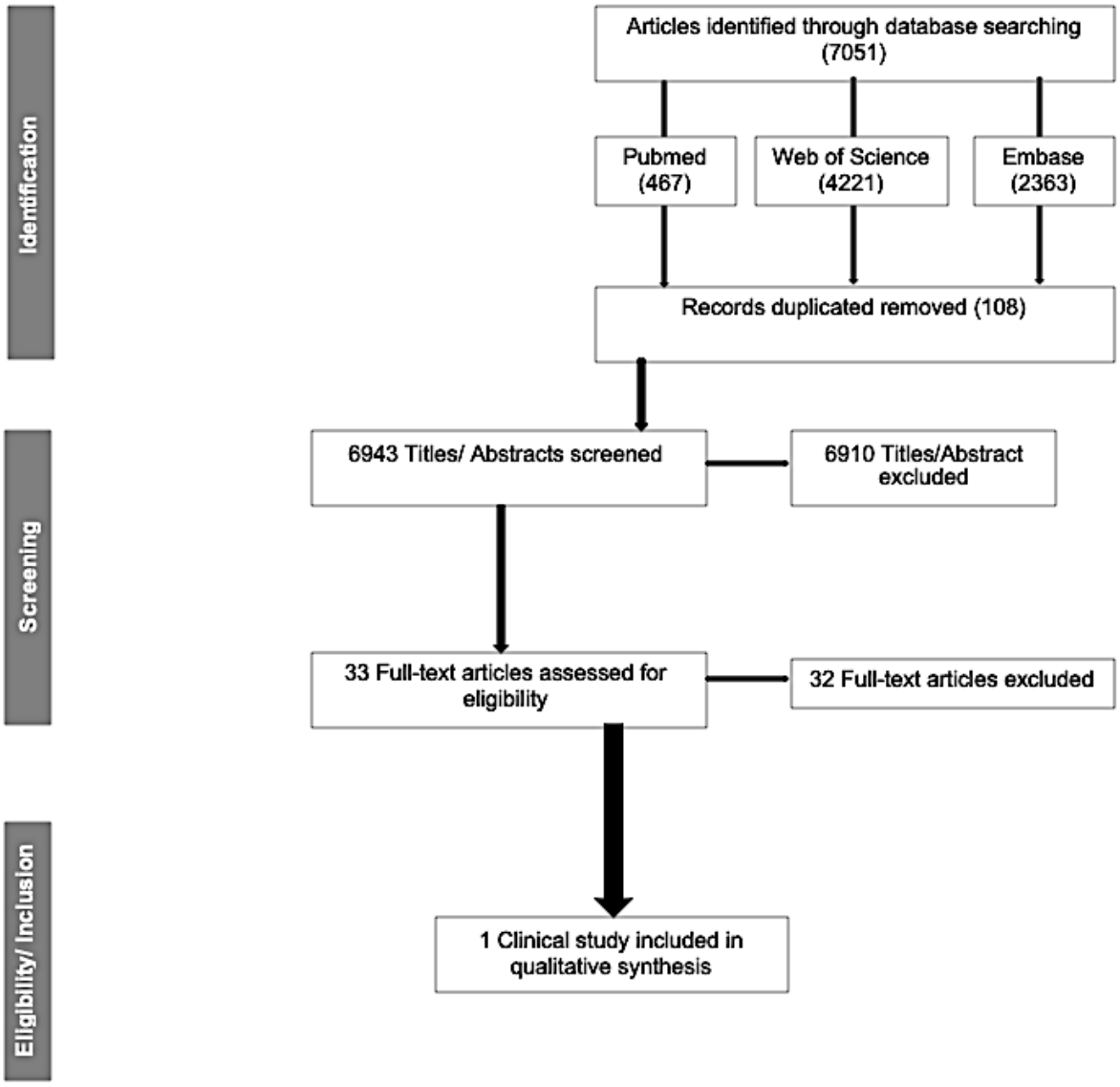

Figure 1. Flow diagram for the search strategy and selection process for the included.

Table 2. Excluded studies and reason for exclusions.

Excluded studies and reason for exclusions	
Author/Year	**Reason for exclusion**
Maciejczyk *et al.,* 2018	Patients with periodontitis were excluded
Trivedi *et al.,* 2018	Blood samples were used instead of salivary samples
Ksiazek *et al.,* 2019	Blood samples were used instead of salivary samples
Perozini *et al.,* 2017	Blood samples were used instead of salivary samples
Cotič *et al.,* 2017	Blood samples were used to obtain serum instead of salivary samples
Hou *et al.,* 2017	Blood samples were used to obtain serum instead of salivary samples
Veisa *et al.,* 2017	Blood samples were used to obtain serum instead of salivary samples
Joseph *et al.,* 2017	Blood samples were used to obtain serum instead of salivary samples
Yoshihara *et al.,* 2016	Blood samples were used to obtain serum instead of salivary samples
Sharma *et al.,* 2016	Blood samples were used to obtain serum instead of salivary samples
Rodrigues *et al.,* 2014	Blood samples were used to obtain serum instead of salivary samples
Grubbs *et al.,* 2017	No biomarkers were analysed
Jamieson *et al.,* 2015	No biomarkers were analysed

Grubbs *et al.,* 2015	No biomarkers were analysed
Garneata *et al.,* 2014	No biomarkers were analysed
Kovalcikova *et al.,* 2019	No biomarkers were analysed
Iwasaki *et al.,* 2019	No biomarkers were analysed
Marinoski *et al.,* 2019	No biomarkers were analysed
Lertpimonchai *et al.,* 201	No biomarkers were analysed
Schmalz *et al.,* 2017	No biomarkers were analysed
Schmalz *et al.,* 2015	No biomarkers were analysed
Nylund, *et al.,* 2015	No biomarkers were analysed
Grubbs *et al.,* 2015	No biomarkers were analysed
Caglayan *et al.,* 2015	No biomarkers were analysed
Oyetola *et al.,* 2015	No biomarkers were analysed
Zhao *et al.,* 2014	No biomarkers were analysed
Machowska *et al.,* 2016	Review
Opatrná, 2015	Review
Demoersman *et al.,* 2018	No clear data about CKD patients
Rodrigues *et al.,* 2016	No direct relation with periodontitis
Pallos *et al.,* 2015	No direct relation with periodontitis
Nylund *et al.,* 2015	Data was updated in 2017, Nylund *et al.,* 2017

Study characteristics and quality assessment

The only article included was a follow-up cross-sectional study, an updated from Nylund *et al.* (2015) with a 157 months follow-up published in *Journal of Periodontology* in 2017.

The original clinical study was published in 2010 by Vesterinen *et al*. who aimed to figure out if diabetic nephropathy affects oral health more than other CKD patients.

This study included a total of 148 patients at predialysis stage, between 2000 and 2005, at the Departments of Oral and Maxillofacial Diseases and Nephrology of the Helsinki University Hospital (HUCH, Finland). Samples of stimulated and non-stimulated saliva were collected, the oral health examination was conducted to all patients by the same dentist, a periodontist. Four patients were excluded as a result of samples missing (n=2) and oral examination status missing (n=2).

A second study was performed by Nylund *et al.* (2015) with the same sample targeting the association between periodontitis and CKD. From this second study an update was made, Nylund *et al.* (2017), where they included a follow-up stage and more biomarkers were analysed.

In Nylund *et al.* (2017) two groups were analysed, predialysis staged patients (CKD stage 4 and 5) and post transplantation stage (follow up). This research analysed salivary samples from the 144 patients. These had been obtained and properly preserved in previous studies between 2000 and 2005, 33 salivary samples dried out or went missing so they analysed samples from 111 predialysis patients. The follow up stage was built with 53 patients exanimated between 2013 and 2015, because 65 died and from the survivors 26 dropped out of the study, 12 salivary samples went missing or dried out so only 41 were analysed.

The study included patients of both sexes, over 18 years old where the median age was 55 at the predialysis group and 60 at the follow-up. 40 patients had Diabetic Nephropathy and 71 had other CKD at predialysis and in the follow-up 8 patients had Diabetic Nephropathy and 33 had other CKD disease.

Patients with smoking habits were included and distinguished, which only 5 (12%) of those patients were current smokers and 11 (27%) were former smokers. The researchers considered that all patients were immunosuppressed. Also, oral

health parameters were taken into consideration like the number of teeth, periodontal pocket depth (PPD), alveolar bone loss, total dental index (TDI), and the periodontal inflammatory burden index (PIBI). All these demographic and clinical parameters were takenintoconsiderationandcombinedwiththebiomarker'smeasures.

The medication quantity was analysed and the HbA1c measures were taken of 87 patients (78.4%) only at the predialysis group. The participants in this group had worse oral health. Sixty-two patients (55.8%) had less than 25 teeth, 98 subjects (88.3%) had more than one site with more or equal to 4mm pocket depth, and 55 (49.5%) of them had a PIBI superior to 5. In matters of bone loss, 28 (25.2%) had a middle bone loss, 11 (9.9%) had an apical loss, and for 44 subjects (39.6%) the TDI was higher than 3. From 111 subjects, 28 (25.2%) were current smokers and 58 (52.2%) never smoked. HbA1c values were higher than 48mmol/mol (6.5%) in 44 patients (39.6%).

At the follow-up stage patients were older and had better oral health, 18 patients had more than one site with more or equal to 4mm pocket depth, 10 patients showed middle bone loss and only 1 had apical bone loss. Remarkably 56% (n=23) of the follow-up patients had a PIBI equal to 0, and 29 subjects had a TDI lower than 2. Thirty-six patients (88%) had a kidney transplant, 4 (10%) were in dialysis, and 1 did not have any replacement therapy.

Nylund et al. (2017) measured and tabulated salivary Triggering Receptor Expressed on Myeloid Cells-1 (sTrem-1), Peptidoglycan recognition protein 1 (PYGLRP1), IL-1β and MMP-8 (Table 3) showing that the 4 analytes had a positive significant relation between them. Also, the values were arranged by the median and interquartile range (IQR) and evaluated the statistical significance.

Periodontal disease associated with salivary biomarkers in CKD patients

As a matter of fact, it is important to referee that demographic characteristic did not have any significance statistical change in the concentration of the salivary biomarkers studied in Nylund et al. (2017), except diabetic nephropathy, who were follow-up patients with higher IL-1β (median equal to 62.00 pg/mL, p=0,015) and at

predialysis current smoke after they made confounders adjustment , influencing IL-1β concentrations. (Table 3)

The clinical oral examination followed a specific criterion given by the World Health Organization (WHO). The median number of teeth present in the oral cavity was 25, in both groups. PPD was classified by the number of sites with equal or more than 4mm probing depth. Alveolar bone loss cervical, middle, or apical were categorized using dichotomic analysis (yes or no). TDI scores at predialysis obtained the median 3 and at follow-up group 2. The PIBI in the predialysis group was categorized in less or equal to 5 or more than 5, and the follow-up group categorized patients as 0 or equal or more than 1.

Amongallpredialysispatients'samplesanalysedinthisincludedinvestigation, the median concentration of sTREM-1 was 180.17 pg/mL, with IQR between 65.31 and 297.38 pg/mL; PGLYRP1 median concentration was 5730.40 pg/ml, with IQR range between 2698.27 and 10874.54 pg/ml; the median concentration of ND IL-1β was 72.20 pg/mL, with IQR between 37.79 and 130.56 pg/mL; and the median concentration of MMP8 in all predialysis patients was not specified (Table 4).

Relating follow-up group, such as predialysis patients median concentration of MMP8 in all patients was also not specified; sTREM-1 was 110.09 pg/mL, with an IRQ of 48.48-243.70 pg/mL; PGLYRP1 median concentration was 6589.92 pg/ml, with an IQR of 2303.60-12273.39 pg/ml; and IL-1βmedianvalueswere71.68pg/mL,withan IQR of 46.65-150.85 pg/mL (Table 5).

Nylund *et al*. (2017) showed that all four biomarkers analysed possessed a positive significant relation ($p<0.001$) among them, specifically between sTREM-1 and PGLYRP1, IL-1βandMMP -8, by virtue a linear regression equal to 0.749, 0.809 and 0.541, respectively.

The predialysis subjects presented higher statistically significant concentrations of salivary PGLYRP1 and IL-1β, and almost significantly higher sTREM-1 concentrations ($p=0.057$) by the fact to possess more teeth in the mouth. It is to denote that MMP-8 levels were nearly the same regardless of the number of teeth (Table 4). When predialysis patient'sdatawereclusteredonPPDmeasures,itdidnot show any significant relation with the changes in those analytes. Conversely, when

the periodontal pockets were 6 mm or deeper in more than 2 sites, they had higher significant salivary concentrations of the studied analytes. The bone loss also influenced the salivary concentration of those biomarkers when advanced (middle and apical regions), showing that patients with bone loss until the cervical region had lower values for the inflammatory markers. The PIBI evaluated the severity of the periodontal condition of the subjects, and independent significant variations occurred in the analysed biomarker's values evidencing a higher concentration of sTrem -1, PYGLRP1, IL-1β,andMMP -8 in patients with the worst condition (PIBI higher than 5) (Table 4).

Regarding the follow-up group, the study showed that neither the TDI values nor the number of teeth present in the mouth had a significant relationship with the concentration of the biomarkers. On the other hand, data relating with the patients' periodontal condition statistic significant changes occurred. When observed periodontal pockets with 4mm or greater in 1 or more sites, it was verified higher sTREM-1, PGLYRP1, and MMP-8 values, and also patients with pockets equal to 6mm or deeper in more than 1 site, showed significantly higher concentrations of PGLYRP1 and IL-1β. Apical alveolar bone loss showed to be an influencing factor in MMP-8 concentration in which patients without bone loss had lower MMP-8 values. Finally, PIBI values equal to or higher than 1 were associated with higher levels of sTREM-1, PGLYRP1 and MMP-8. (Table 5)

Unfortunately, in Nylund *et al.* (2017) there is no relation between the biomarker's levels and the death of some subjects.

Discussion

The current systematic review was designed to gather the most recent data about the possible association between chronic kidney disease and periodontitis / periimplantitis by analysing salivary biomarkers. As far as we know, a systematic review has never been carried out in this context. Currently, it is recognized that inflammatory response caused by a periodontal infection can be disseminated froth all organic system, so it is important to conduct studies associating oral and systematic diseases to improve therapeutic prognosis, trying to suggest a more specific treatment. Therefore, the elaboration of this work is significant for all clinicians to gather updated synthesizing the knowledge and to be another tool for efficient therapies analysis.

A vast number of articles researched on three of the major bibliographic data platforms were thoroughly analysed to include the largest possible number of studies carried out in the area of interest in this systematic review. It was detected that there are a reasonable number of authors studying the relation between CKD and periodontitis. Some of them analysed blood and serum samples with the objective to support a relation between these two diseases but only one study, and its follow-ups were found where saliva analysis was performed. Saliva shows to be an efficient way to diagnose oral and systemic disorders, it is easier to collect and store when compared with blood(17,19,21,23,51–56). Furthermore, saliva is not related with the stress of the needle use, that could be a plus in the daily practice and when conducting a study, so it would be important to do more research using saliva to reinforce its applicability. (16,17)

This systematic review aimed to study, not only patients with periodontitis but also patients with periimplantitis. No study addressing peri-implantitis and following the inclusion criteria was found. This may be due to the low quality of life of patients with CKD and to the fact that most of these patients tend to neglect their oral hygiene due to concern for overall health and the emotional problems related to the kidney disease itself. (1,3,64,10,57–63) (1,3,10,57–64) In another way, implants tend to be more and more used as a rehabilitating therapy for edentulous spaces. In periimplantitis cases literature shows that inflammatory biomarkers are present in systemic inflammation.(31,65,66) Teixeira *et al*., 2019 shown that sTREM-1, PGLYRP1 and MMP-8 are involved in periimplantitis, this 3 analytes were analysed in

the included study regarding the patients with CKD and periodontitis.(67) Therefore, periimplantitis can be a cause of continuous systemic inflammation that can lead to several problems in patients with CKD.(31,65,66) Studies must be conducted in this area of interest.

Nylund *et al.,* 2017 was a study conducted at the Department of Oral and Maxillofacial Diseases and Nephrology of the Helsinki University Hospital in Finland using the same samples of previous studies and with the same ethical committee, patients samples were collected between the years of 2000 and 2005, consequently follow-up samples were collected between 2013 and 2013. Within this fifteen-years study, some samples were lost or made infeasible, it was unfortunate. Moreover, over the years no new patients have been added to the study in order to increase the sample and significance of the data.

In the included study the participants selection was very well defined. Individuals with less than 18 years, pregnant or breastfeeding women, handicapped (physically or mentally disabled), and prisoners were excluded from the research. These restrictions are important when trying to standardize the studied individuals due to the specific features of the paediatric age.(68) Also, pregnant women face physiologic and hormonal changes that could influence the results.(69,70) Likewise, in the physically or mentally disabled some specific oral alterations occur, and when motor alterations are present patients tend to have trouble performing their own oral hygiene.(71,72)

The predialysis group was constituted by patients at stages 4 and 5 and the follow-up group was constituted with post transplantation patients. The problem is that in follow-up group one individual, due to bad general health, never received the transplant and 3 patients rejected their transplant so the 4 individuals continued in dialysis. Due to all oral and systemic changes that dialysis causes, this small group of patients may have introduced bias when studying the follow up group results. (2,7,9-13) Some researchers have shown that the concentrations of some metabolites in saliva differ according to the degree of renal failure and treatment with dialysis so it would be important to extend the studies to patients with other stages of the disease and to compare the differences between them.(2,32)

Regarding the periodontal condition, patients were distinguished between having zero sites with 4 mm or more pocket depth and one or more sites with 4mm or deeper, this means that patients were distinguished in having or not moderated/advanced periodontists. This study was published in 2017, at the same year a new periodontal disease classification was approved so it would be eligible to have used the new classification in this study. Therefore, it would be interesting to differentiate the periodontal condition between patients without periodontitis and with periodontitis according to its stage.

When studying the influence of one disease in another it is important to remove or distinguish factors that can influence the results like demographic characteristics and general health pathologies. Fortunately, demographic characteristic did not have any statistical significance except diabetic nephropathy and at predialysis group current smokers, that is important to remove bias when evaluating clinical characteristics.

Diseases and proteins-related

CKD and periodontitis are two chronic diseases that can be influenced by other systemic illnesses like diabetes, hereupon the measure of glycated haemoglobin (HbA1c) is important to be obtained. In the included study, HbA1c measures were only taken in patients at the predialysis stage, because the periodontal index was the worst, and the values between diabetic nephropathy patients and other CKD patients were very similar, such as when comparing values between patients with HbA1c lower or over 48 mmol/mol (≈6.5%). Nevertheless, the authors distinguish diabetic nephropathy from other types of CKD, which had very significant values found at the follow-up stage patients, with higher IL-1βthatisusualforpatientswithdiabetes,once that IL-1βhasanimpacti n the pathogenesis of diabetes and leads to problems related with CKD (73,74). The follow-up patients were reported as having better oral hygiene with lower values of salivary sTREM-1, PYGLRP1, IL-1β,andMMP -8, which can lead to follow question: are these high levels of salivary biomarkers, mainly IL-1β,caused by diabetes and not suffered the influence of the periodontal disease? Some studies relate periodontal therapy to the reduction of these inflammatory biomarkers and the consequent reduction of systemic inflammation (14,17,31,83,95,99–105).

Thus, it emerges a question if the worst periodontal index might be the cause of the similar systemic concentration of IL-1β aliketothatofpatientswithdiabetes.It was showed that periodontitis influences on those systemic values of this biomarker leading to a higher systematic inflammation, causing problems in the general patient status with chronic kidney disease (31,75–77).

Either in CKD as in periodontitis, beyond IL-1β thatisaknownproinflammatory and induce destructive tissue behaviour (17,75–85), the study verified the MMP-8, PGLYRP1, and sTREM-1, similarly proinflammatory proteins normally found in chronic illness. Nylund *et al*. (2017) showed, by salivary biomarkers, a positive and significant correlation between sTREM-1, PYGLRP1, IL-1β, and MMP -8 ($p<0.001$), which was confirmed recently by Silbereisen *et al*. (2019). Besides, the PGLYRP1 works like a ligand that activates TREM-1 (67,80,81,86,87) and IL-1β and MMP -8 also have an interrelation, MMP-8 is responsible for the proteolytic cleavage of membrane-bound delivering of sTREM-1 to the circulation and IL-1β is produced and released due to the proinflammatory response of sTREM-1 (80,81,83,85,88). Interestingly, only the median concentration of MMP8 in all predialysis and follow-up patients was undescribed, being considered as a serious failure, because it is proved that MMP-8 is present in the acute phase of periodontitis having a rule in the pathogenesis of this disease (39,85,91–93) and can be used as a biomarker in periodontitis diagnose (39,85,92).

A saliva analysis was performer in order to find these biological markers, but they can also be found in the bloodstream. Saliva is secreted by salivary glands that are in direct contact with capillaries, this means that biomarkers exchanges between the circulatory system and saliva occur by the epithelial cells due to a diffusion gradient.(18,37,73) Since these biomarkers circulate throughout the body, a relation can be made between there changes and the oral and systemic conditions.

Rudick *et al.,* 2017, like others authors, stated that TREM-1 is upregulated in the presence of periodontal inflammation and that it can be used as a biomarker of inflammation providing a link between oral and systemic inflammation.(31,74–76) In this study, due to the non-use of a healthy control group, conclusion cannot be made regarding the higher values of sTREM-1 due to the CKD, but some studies show that it occurs.(77) Like other authors reported, the results of the analysed study showed

that in cases of periodontitis the concentration of sTREM-1 was significantly higher, meaning that periodontitis is an independent cause of the higher levels of sTREM-1 in these patients.(74,75) TREM-1 is a systemic inflammatory factor, for this reason higher values can lead to or worsen the prognosis of several diseases like rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases, type 1 diabetes, and psoriasis cystic fibrosis, sepsis and even to atherosclerotic complications, one of the main causes of mortality in patients with CKD. (41,78,79) Therefore sTREM-1 is an important biomarker to demonstrate that there are high values of systemic inflammation and in the early detection of untreated periodontitis.

Results showed that in predialysis group, PGLYRP1 was significantly higher in cases of patients with more than 25 teeth, middle and apical bone, PIBI higher than 5 and a TDI higher than 3, it means that this biomarker was higher in cases with horst oral health and periodontitis. Studies have shown that in the presence of a poor oral health and periodontitis, like predialysis subjects, PGLYRP1 appears to be elevated.(75,80) At the follow up group patients had best oral health but the ones with higher PPD and PIBI had significant higher levels of this analyte, supporting that PGLYRP1 is higher in periodontitis. PGLYRP1 works like a ligand that activates TREM-1 during infection, so the high values of this marker indicate that the patient probably is suffering of systematic inflammation due to periodontitis. This can lead to systemic problems like the ones mentioned correlated with TREM-1. (67,75,77–80)

It is proved that MMP-8 is present in the acute phase of periodontitis having a rule in the pathogenesis of this disease. (39,81–84) It can also be used as a biomarker in periodontitis diagnosis. (39,81,83) In cases of periodontitis the study showed that the values tend to be significantly higher, also in presence of middle and apical bone loss at the predialysis stage values were significantly higher. Through these results we can support that MMP-8 appears to be up regulated in cases of periodontitis, thus it can be a systemic inflammation generator once that it is correlated with the activation of several systemic inflammatory markers like TREM-1.(67,74,81) Studies showed that periodontal therapy leads to a reduction of the inflammatory load. Therefore, this is important in reducing the systemic inflammation in patients with CKD and most continue to be studied, as it can lead to systemic problems like coronary artery disease

and also to the development of the of kidney diseases themselves.(42,67,81,83,85–87)

IL-1β appeared to be significantly higher in cases where predialysis patients had periodontitis with an apical bone loss and a PIBI over 5. It also happened in cases where TDI was higher than 3. These results were expected, since that this proinflammatory protein is one of the responsible for the bone resorption induction in periodontitis (39,79,85,93,96). IL-1β has a positive correlation with TREM -1 and PGLYRP1, that can be explained because it is a downstream molecule of the signalling pathway of TREM-1 (90), which supports the results obtained in the included study. The high levels of this interleukin can be caused by the kidney injury itself. Otherwise, the study results showed statistically significant values showing that they were caused by periodontitis which induced a major systemic inflammation (17,79,92,95–98). IL-1β regulates the metabolism of kidney stromal contributing to kidney fibrosis, it also is linked with cardiovascular diseases, thus periodontitis could be a possible initiator of diseases linked with the death of CKD patients (42,79,92,97,98).

Other considerations

Nylund *et al*. (2017) did not compare the results obtained from the two groups (predialysis and follow-up) with any healthy control group, justifying that the follow-up stage data is enough to help and compare with the results of the predialysis group. The importance of comparing these two groups is based on they have different oral health, highlighting the importance of the periodontal treatment for the patients, even during the predialysis phase, which would reduce the focal inflammation. It would be interesting to have more studies along these perspectives but adding a healthy control group to support and reinforce the importance of periodontal therapy in reducing systemic inflammation.

They showed that follow up stage had better oral hygiene and consequently lower values of salivary sTREM-1, PYGLRP1, IL-1β and MMP-8. There are studies that relate periodontal therapy to the reduction of these inflammatory biomarkers and the consequent reduction of systemic inflammation.(14,17,93,94,31,74,87–92) It

would be interesting to have more studies along these lines that in addition to a follow-up group there was a healthy control group to support and reinforce the importance of periodontal therapy in reducing systemic inflammation.

In the included study, only 4 analytes were studied. In future studies, it is suggested including other salivary biomarkers to be analysed, such as IL-6, IL-8, TNF-α,MCP -1, C-reactive protein, among other biomarkers as used by Pallos *et al*., which involve either oral diseases as systemic inflammations (17).

The only included study concluded that early detection of periodontitis would be beneficial to postpone progression of CKD by reducing the systemic inflammation provoked by it. The biomarkers analysed can indicate high systemic inflammatory burden, important in the prevention of cardiovascular complications and consequent decrease of mortality.

Conclusion

For the enrichment of knowledge, this is the first systematic review that evaluates the current evidence of the association between chronic kidney disease and periodontitis / periimplantitis by the analysis of salivary biomarkers. Only one study fulfilled the inclusion criteria for this systematic review. By the results obtained, we realize the importance of this type of study due to the systemic inflammation caused by the increase of proinflammatory response in the presence of periodontitis. Only one article with this methodology is not enough to establish a direct cause effect association between periodontitis and CKD or vice-versa, but we conclude that an effect can be caused, as theconfounder'sanalysesshowedanindependentinfluence of periodontitis among the analysed proinflammatory biomarkers. Therefore, more randomized controlled trials should be performed in this area of interest due to the potential of salivary biomarkers in an easier detection of those diseases and the possibility of having a more predictable prognosis during the treatment of patients with CKD by controlling the persistent systematic inflammation caused by periodontal disease using traditional periodontal treatment and targeted therapies.

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Attatchemnts

Table 3, predialysis stage

Demographic characteristic

		sTREM-1 (pg/mL)	IQR (25th-75th)	P*	PGLYRP1 (pg/mL)	IQR[‖] (25th-75th)	P*	IL-1ß (pg/mL)	IQR[‖] (25th-75th)	P*	MMP-8 (ng/mL)	IQR[‖] (25th-75th)	P*
CKD Diagnosis[†]	Diabetic Nephop. (N=40)	174,00	(81,01-297,15)		5825,43	(3498,70-13640,20)		72,57	(36,83-176,01)		147,92	(68,74-185,14)	
	Other CKD (N=71)	183,35	(50,89-301,68)	0,742	5727,70	(2169,00-10599,11)	0,089	72,20	(38,27-130,31)	0,679	116,47	(48,95-203,4)	0,630
HbA1c values[††]	<48mmol/mol (N=43)	177,23	(41,25-275,42)		5903,20	(2080,90-10509,10)		72,20	(26,63-126,80)		86,37	(42,22-186,66)	
	≥48mmol/mol (N=43)	183,44	(81,01-323,98)	0,310	6132,74	(3498,70-14067,44)	0,083	84,89	(37,84-180,59	0,312	144,78	(63,43-185,14)	0,373
Smoking[§]	Yes (N=28)	195,46	(88,49-408,70)		6181,70	(3177,65-14096,13)		111,60	(45,12-187,27)		120,24	(15,97-179,82)	
	No (n=58)	174,00	(56,60-272,98)	0,139	5719,32	(2681,67-9974,20)	0,302	61,65	(38,15-100,31)	0,050	127,80	(60,70-195,68)	0,371
Age (median)	≤55 years (N=60)	183,35	(94,69-314,33)		7151,42	(3160,51-12034,47)		76,46	(43,61-125,97)		121,64	(69,17-212,36)	
	>55 years (N=51)	175,73	(48,77-275,43)	0,306	4615,96	(2169,00-10139,77)	0,065	67,97	(35,19-138,77)	0,396	132,87	(40,42-185,97)	0,309
Sex	Male (N=72)	175.61	(67,22-314,33)		5635,33	(2818,76-11243,03)		78,98	(37,37-138,67)		113,19	(64,18-202,16)	
	Female (N=39)	183,35	(62,27-242,88)	0,926	5903,20	(2631,88-10083,70)	0,966	66,85	(38,28-126,80)	0,521	117,40	(48,95-186,66)	0,533
Medication (median)	≤8 (N=59)	183,35	(48,77-318,94)		5727,07	(2080,90-10509,09)		67,97	(36,09-122,31)		116,47	(62,12-180,95)	
	>8 (N=52)	178,79	(76,42-283,38)	0,974	6025,79	(3346,95-12441,78)	0,107	86,55	(38,62-159,61)	0,338	137,20	(42,60-202,16)	0,587

Clinical parameters characteristic

		sTREM-1 (pg/mL)	IQR[‖] (25th-75th)	P*	PGLYRP1 (pg/mL)	IQR[‖] (25th-75th)	P*	IL-1ß (pg/mL)	IQR[‖] (25th-75th)	P*	MMP-8 (ng/mL)	IQR[‖] (25th-75th)	P*
Median nº of teeth	≤25 (N=62)	163,37	(42,38-272,57)		4504,47	(2416,72-9293,84)		61,42	(34,91-120,72)		126,07	(36,10-195,84)	
	>25 (N=49)	197,86	(107,51-324,78)	0,057	9037,47	(3245,89-13125,59)	**0,009**	90,41	(45,91-161,48)	**0,040**	124,00	(84,98-183,81)	0,389
PPD[ǀ] (sites)	No periodontal pockets ≥4mm (N=13)	121,26	(70,68-235,79)		5727,07	(2775,13-11018,17)		84,37	(34,86-122,95		106,14	(39,03-192,21)	
	1 or more, pockets with ≥4mm (N=98)	184,23	(61,50-308,09)	0,494	5825,43	(2681,67-10766,87)	0,927	71,01	(38,15-138,48)	0,869	134,60	(60,70-193,74)	0,762
Alveolar bone loss[*] – Cervical	Yes (N=55)	183,35	(76,04-301,68)		6615,55	(2831,24-11270,10)		72,20	(37,79-138,77)		124,00	(42,22-182,64)	
	No (N=47)	167,67	(59,20-298,38)	0,584	5559,08	(2440,85-10361,29)	0,359	74,01	(38,27-123,46)	0,933	119,27	(67,30-203,48)	0,608
Alveolar bone loss[*] – Middle	Yes (N=28)	204,55	(88,18-421,01)		9629,56	(5191,51-13929,80)		98,11	(39,67-188,08)		151,37	(74,16-219,72)	
	No (N=74)	169,25	(64,55-272,57)	0,160	4633,00	(2426,51-9988,22)	**0,008**	68,44	(37,09-111,77)	0,143	117,23	(59,91-181,31)	0,345
Alveolar bone loss[*] – Apical	Yes (N=11)	293,45	(98,83-473,93)		13933,90	(6517,81.20259,72)		183,51	(79,37-251,44)		182,39	(145,80-203,92)	
	No (N=91)	174,00	(59,21-278,70)	**0,026**	5559,08	(2440,85-10361,29)	**0,006**	67,95	(36,71-122,31)	**0,011**	116,47	848,95-180,95)	**0,028**
PIBI[‡]	≤5 (N=56)	115,49	(36,00-237,82)		3434,49	(18,36,32-8807,48)		50,13	(25,64-98,82)		86,45	(32,76-163,41)	
	>5 (N=55)	207,45	(127,63-370,58)	**0,001**	8973,89	(4360,92-14048,66)	**<0,001**	96,88	(52,51-188,52)	**<0,001**	155,00	(102,17-202,32)	**0,004**
TDI[#] (median)	≤3 (N=58)	141,72	(50,36-141,75)		4513,38	(2230,81-9661,76		63,83	(35,96-106,35)		111,07	(40,44-164,44)	
	>3 (N=44)	212,53	(102,35-352,34)	**0,032**	8936,45	(3548,82-14015,87)	**0,005**	89,11	(43,34-181,98)	**0,037**	153,68	(69,83-203,53)	**0,049**

[*] *P- values* <0,05 are bolded as statistically significant values (obtain from Mann-Whitney U test)
[†] CKD patients total (N= 111). Diabetic nephropathy patients (N=40), Other CKD patients (N=71)
[††] HbA1c values available from 87 patients. HbA1c = 48mmol/mol ≈ 6,5%; HbA1c <48mmol/mol (N=43), HbA1c ≥48mmol/mol (N=44)
[§] Current smokers (N=28), non-smokers (N=58). Former smokers were excluded (N=25)
[‖] IQR= interquartile range. (25th value – 75th value) when organized from the lowest to the highest to find the median.
[*] Alveolar bone loss: bone loss in any sextant to cervical, middle or apical thirds of the root lengths
[‡] Periodontal Inflammatory Burden Index
[#] Total Dental Index
[ǀ] Periodontal Pocket Depth

Table 4, Follow-up

		Demographic characteristic											Clinical parameters characteristic												Alveolar bone loss									
		sTREM-1 (pg/mL)	IQR[i] (25th-75th)	P*	PGLYRP1 (pg/mL)	IQR[i] (25th-75th)	P*	IL-1ß (pg/mL)	IQR[i] (25th-75th)	P*	MMP-8 (ng/mL)	IQR[i] (25th-75th)	P*	sTREM-1 (pg/mL)	IQR[i] (25th-75th)	P*	PGLYRP1 (pg/mL)	IQR[i] (25th-75th)	P*	IL-1ß (pg/mL)	IQR[i] (25th-75th)	P*	MMP-8 (ng/mL)	IQR[i] (25th-75th)	P*	Median n° of teeth		PPD[j] (sites)		Cervical		Middle		Apical		TDI[#] (median)		PIBI[‡]	
																										≤25 (N=25)	>25 (N=16)	No periodontal pockets ≥4mm (N=23)	1 or more, pockets with ≥4mm (N=16)	Yes (N=24)	No (N=17)	Yes (N=10)	No (N=31)	Yes (N=1)	No (N=40)	≤2 (N=29)	>2 (N=12)	0 (N=23)	≥1 (N=18)
CKD Diagnosis	Diabetic Nephop. (N=8)	169,77	(82,92-376,97)		15995,00			142,11	(82,01-255,90)		45,70	(16,70-440,58)		110,09	(71,72-245,28)		4692,18	(2075,38-18257,12)		79,64	(49,10-162,73)		31,40	(3,45-133,75)												
	Other CKD (N=33)	106,89	(43,66-231,80)	0,409	4322,75	(2075,38-9516,17)	0,073	62,00	(35,49-144,98)	**0,015**	58,90	(4,00-65,75)	0,355	94,08	(41,66-248,46)	0,741	6748,78	(2792,10-9742,23)	0,926	62,22	(43,22-136,95)	0,588	67,75	(6,00-102,05)	0,802										
Renal replacement[¤]	Dialysis (N=4)	116,47	(102,90-153,11)		6661,67	(4338,44-8110,37)		83,91	(49,79-69,60)		78,85	(36,40-120,48)		66,91	(26,80-121,26)		3845,86	(1510,53-7405,30)		62,45	(27,05-111,92)		10,90	(2,30-78,90)												
	Transplant (N=36)	107,69	(41,66-263,92)	0,948	6048,74	(2234,97-13888,76)	0,983	60,63	(43,22-167,51)	0,472	30,30	(4,00-111,35)	0,394	167,45	(114,87-453,73)	**0,004**	9606,62	(4297,19-18619,65)	**0,004**	119,68	(54,18-198,00)	0,066	102,60	(17,88-252,08)	**0,004**										
Smoking‡	Yes (N=5)	66,91	(4,55-366,26)		7004,04	(2308,71-12171,67)		87,70	(31,70-142,51)		74,30	(1,45-134,90)		106,89	(49,26-195,26)		5326,67	(1913,25-9692,38)		66,12	(33,27-162,73)		20,60	(4,00-94,60)												
	No (n=25)	121,26	(48,48-260,35)	0,385	6589,92	(2780,92-10413,41)	1,000	79,64	(47,54-162,73)	0,666	51,40	(5,40-98,90)	0,872	116,47	(48,08-296,88)	0,534	6748,78	(2492,12-14429,44)	0,525	75,90	(46,87-147,53)	0,832	67,75	(5,25-168,33)	0,218										
Age (median)	≤60 years (N=21)	116,47	(38,03-285,73)		8394,30	(3711,64-16355,46)		91,52	(51,57-207,98)		61,20	(6,30-165,75)		107,69	(71,72-229,81)		3433,23	(1948,83-14196,10)		60,65	(41,98-198,00)		22,00	(2,75-149,45)												
	>60 years (N=20)	107,69	(38,03-213,92)	0,620	4271,64	(1877,67-8110,37)	0,112	60,63	(31,52-109,51)	0,064	21,15	(2,80-104,45)	0,192	116,47	(39,65-253,22)	0,964	6764,69	(3577,42-11039,36)	0,410	80,11	(46,20-148,55)	0,731	58,90	(50,70-105,20)	0,687										
Sex	Male (N=27)	110,09	(39,65-223,07)		5326,67	(2440,85-13507,41)		71,68	(42,22-148,55)		58,90	(4,60-106,30)		560,26	(560,26-560,26)		18858,25			267,33			532,20												
	Female (N=14)	110,88	(65,71-305,17)	0,596	6796,98	(2120,86-12594,09)	0,776	72,88	(49,89-181,70)	0,577	21,15	(4,00-122,20)	0,968	108,49	(48,08-232,99)	0,244	5958,29	(2234,97-10726,39)	0,244	68,91	(46,44-1047-78)	0,195	45,70	(4,15-106,03)	**0,049**										
Medication (median)	≤9 (N=25)	119,66	(43,66-271,46)		5326,67	(2212,63-12273,39)		87,70	(47,54-162,73)		10,90	(4,00-104,05)		106,89	(48,48-243,70)		4692,18	(2303,60-10322,96)		63,37	(44,21-149,32)		31,40	(4,85-105,75)												
	>9 (N=26)	103,70	(66,91-167,45)	0,404	6884,37	(2564,90-12913,55)	0,843	62,70	(31,74-107,66)	0,361	76,60	(19,4-120,48)	0,197	143,55	(39,23-371,02)	0,601	7674,72	(2321,71-19705,43)	0,403	91,29	(55,85-203,34)	0,403	85,75	(3,18-201,93)	0,513										
														66,91	(26,80-121,26)		3845,86	(1510,53-7405,30)		62,45	(27,05-111,92)		10,90	(2,30-78,90)										
														167,45	(114,87-453,73)	**0,004**	9606,62	(4297,19-18619,65)	**0,004**	119,68	(54,16-198,00)	0,066	102,60	(17,88-252,08)	**0,004**										

* *P. values* <0,05 are bolded as statistically significant values (obtain from Mann-Whitney U test)
‡Current smokers (N=5), non-smokers (N=25). Former smokers were excluded (N=11)
[i] IQR= interquartile range. (25th value – 75th value) when organized from the lowest to the highest to find the median.
[¤]One patient did not have any renal placement therapy, excluded from here
[j]Periodontal Inflammatory Burden Index
[#]Total Dental Index
[‡]Periodontal Pocket Depth

Kidney Research and Clinical Practice

Assessment of Salivary Protein Profile in patients with Chronic Kidney Disease-associated to Periodontal disease: A Systematic review

--Manuscript Draft--

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Abstract:	Background: Chronic kidney disease (CKD) is a chronic inflammatory illness with progressive and irreversible changes at the kidney function. Periodontitis is the most prevalent chronic inflammatory oral disease worldwide. Authors have proposed that periodontal inflammation spreads systemically being associated with CKD patients. Salivary biomarkers have a great potential in the diagnosis and correlation of both diseases and can also be important in monitoring the systemic inflammation. Therefore, this study aimed to analyze the association between CKD and periodontitis by salivary biomarkers assessment. Methods: Systematic review was conducted analyzing the salivary proteins described in the literature in patients with CKD and periodontitis. A electronic search through PubMed, EMBASE, and Web of Science databases was conducted by independent reviewers to identify clinical studies performed in humans published between January 2009 and January 2020, with no geographical or language restrictions. The basic terms used were: “chronic kidney disease”, periodontitis, “periodontal disease”, “inflammatory biomarkers”, “salivary biomarkers”. Results: Search strategy identified 7051 protentional eligible articles. After adequate evaluation, only one met all the inclusion and exclusion criteria. The included article had a low risk of bias in the quality assessment (PROBAST) and 4 salivary biomarkers were studied (sTrem-1, PYGLRP1, IL-1β, and MMP-8) in patients at the predialysis stage and in the follow-up. Study results, by a confounders analysis, showed that periodontitis had a significant influence on increasing the values of these inflammatory biomarkers. Conclusion: There is an association between the two chronic inflammatory diseases studied, CKD and periodontitis, after analysis of the proinflammatory biomarkers.

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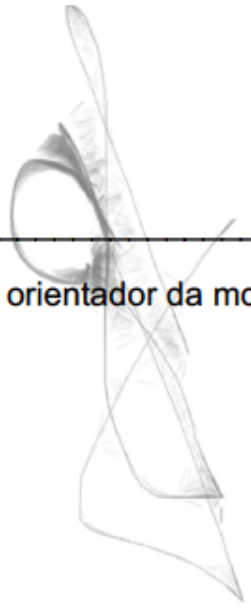
Declaração de cumprimento anti - plágio

Eu, Gustavo Vicentis de Oliveira Fernandes, orientador da monografia intitulada Salivary protein in patients with Chronic Kidney Disease-associated to periodontal and peri-implant disease: Systematic review, confirmo que o trabalho apresentado foi analisado na plataforma *"Turnitin"* e apresenta um índice de similaridade 6% cumprindo os requisitos anti plágio definidos.

Viseu, 27/07/2020



(O orientador da monografia)