

NARA SARMENTO MACEDO SIGNORELLI

**Impacto sistêmico das periodontites apicais: uma
revisão de escopo e relato de caso**

Systemic impact of apical periodontitis: a scope review and case report

Dissertação apresentada à Faculdade de Odontologia da
Universidade de Uberlândia, para obtenção do Título de
Mestre em Odontologia na Área de Clínica Odontológica
Integrada.

Uberlândia

2023

NARA SARMENTO MACEDO SIGNORELLI

**IMPACTO SISTÊMICO DAS PERIODONTITES
APICAIS: UMA REVISÃO DE ESCOPO E
RELATO DE CASO**

Systemic impact of apical periodontitis: a scope review and case report

Dissertação apresentada à Faculdade de Odontologia da
Universidade de Uberlândia, para obtenção do Título de
Mestre em Odontologia na Área de Clínica Odontológica
Integrada.

Orientadora: Prof^ª. Dr^ª. Camilla Christian Gomes Moura

Banca Examinadora:

Prof^ª. Dr^ª. Camilla Christian Gomes Moura

Prof. Dr. Luiz Renato Paranhos

Prof^ª. Dr^ª. Graziela De Luca Canto

Prof^ª. Dr^ª. Priscila Barbosa Ferreira Soares

Prof^ª. Dr^ª. Renata Pereira Georjutti

UBERLÂNDIA

2023



UNIVERSIDADE FEDERAL DE UBERLÂNDIA
Coordenação do Programa de Pós-Graduação em Odontologia
Av. Pará, 1720, Bloco 4L, Anexo B, Sala 35 - Bairro Umuarama, Uberlândia-MG, CEP 38400-902
Telefone: (34) 3225-8115/8108 - www.ppgoufu.com - copod@umuarama.ufu.br

**ATA DE DEFESA - PÓS-GRADUAÇÃO**

Programa de Pós-Graduação em:	Odontologia				
Defesa de:	Dissertação de Mestrado Acadêmico, nº 422, PPGODONTO				
Data:	Treze de Julho de Dois Mil e Vinte e Três	Hora de início:	14:00	Hora de encerramento:	15:42
Matrícula do Discente:	12122ODO023				
Nome do Discente:	Nara Sarmento Macedo Signorelli				
Título do Trabalho:	Impacto sistêmico das periodontites apicais: Uma revisão de escopo e relato de caso				
Área de concentração:	Clínica Odontológica Integrada				
Linha de pesquisa:	Processo de Reparo				
Projeto de Pesquisa de vinculação:	Processo de Reparo				

Reuniu-se em Web Conferência pela plataforma Zoom, em conformidade com a PORTARIA Nº 36, DE 19 DE MARÇO DE 2020 da COORDENAÇÃO DE APERFEIÇOAMENTO DE PESSOAL DE NÍVEL SUPERIOR - CAPES, pela Universidade Federal de Uberlândia, a Banca Examinadora, designada pelo Colegiado do Programa de Pós-graduação em Odontologia, assim composta: Professores Doutores: Graziela de Luca Canto (UFSC); Luiz Renato Paranhos (UFU); Camilla Christian Gomes Moura (UFU); orientador(a) do(a) candidato(a).

Iniciando os trabalhos o(a) presidente da mesa, Dr(a). Camilla Christian Gomes Moura, apresentou a Comissão Examinadora e o candidato(a), agradeceu a presença do público, e concedeu ao Discente a palavra para a exposição do seu trabalho. A duração da apresentação do Discente e o tempo de arguição e resposta foram conforme as normas do Programa.

A seguir o senhor(a) presidente concedeu a palavra, pela ordem sucessivamente, aos(às) examinadores(as), que passaram a arguir o(a) candidato(a). Ultimada a arguição, que se desenvolveu dentro dos termos regimentais, a Banca, em sessão secreta, atribuiu o resultado final, considerando o(a) candidato(a):

Aprovada.

Esta defesa faz parte dos requisitos necessários à obtenção do título de Mestre.

O competente diploma será expedido após cumprimento dos demais requisitos, conforme as normas do Programa, a legislação pertinente e a regulamentação interna da UFU.

Nada mais havendo a tratar foram encerrados os trabalhos. Foi lavrada a presente ata que após lida e achada conforme foi assinada pela Banca Examinadora.



Documento assinado eletronicamente por **Camilla Christian Gomes Moura, Professor(a) do Magistério Superior**, em 13/07/2023, às 15:43, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#).



Documento assinado eletronicamente por **Luiz Renato Paranhos, Professor(a) do Magistério Superior**, em 13/07/2023, às 15:43, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#).



Documento assinado eletronicamente por **Graziela De Luca Canto, Usuário Externo**, em 17/07/2023, às 16:04, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#).



A autenticidade deste documento pode ser conferida no site https://www.sei.ufu.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **4647180** e o código CRC **861C30CE**.

Ficha catalográfica

Ficha Catalográfica Online do Sistema de Bibliotecas da UFU
com dados informados pelo(a) próprio(a) autor(a).

S578 2023	Signorelli, Nara Sarmento Macêdo, 1988- Impacto sistêmico das periodontites apicais: uma revisão de escopo e relato de caso [recurso eletrônico] : Systemic impact of apical periodontitis: a scope review and case report / Nara Sarmento Macêdo Signorelli. - 2023. Orientadora: Camilla Christian Gomes Moura. Dissertação (Mestrado) - Universidade Federal de Uberlândia, Pós-graduação em Odontologia. Modo de acesso: Internet. Disponível em: http://doi.org/10.14393/ufu.di.2023.389 Inclui bibliografia. Inclui ilustrações. 1. Odontologia. I. Moura, Camilla Christian Gomes, 1979-, (Orient.). II. Universidade Federal de Uberlândia. Pós-graduação em Odontologia. III. Título. CDU: 616.314
--------------	---

Bibliotecários responsáveis pela estrutura de acordo com o AACR2:
Gizele Cristine Nunes do Couto - CRB6/2091
Nelson Marcos Ferreira - CRB6/3074

DEDICATÓRIA

Dedico à minha Malu.

Inspiração e energia para meus passos incertos à caminho do melhor que possa ser.

AGRADECIMENTOS

Agradeço ao tempo, que amadureceu minha caminhada e meus pensamentos, transformando minha jornada dentro da Odontologia, na docência e, por fim, na pesquisa.

Agradeço à Deus, que apesar de ter me feito com a cabeça nas nuvens e completamente inquieta, soube colocar propósitos em meu coração que mantiveram meu foco e alimentaram minha sede por aprender e descobrir.

Agradeço aos meus pais, Maria Edith e Rosembergue, que estão sempre superando seus desejos internos do que gostariam que eu fosse para aceitar e aplaudir o que eu decidi ser. Por me amarem acima de tudo e por terem acendido em mim o prazer pelo estudo, pela leitura e valorizado minha curiosidade como qualidade. Obrigada pelas orações mãe. Obrigada pelas conversas pai.

À minha irmã Larissa, extensivo a família que ela me deu, Flávio e meus pequenos imensos amores Antônio e Daniel, vocês são casa, abraço e lar. A aceitação que tenho com vocês à todas às minhas limitações e a confiança que mesmo assim depositam em mim são muitas vezes combustível para continuar. Amo vocês com toda minha vida.

Ao meu irmão Rodolpho, que é das poucas pessoas que de alguma forma sempre me admirou e confiou em mim.

Agradeço ao meu marido, Luiz Fernando, que em todos os momentos foi apoio, abdicação e olhos brilhantes de orgulho. Não sei se palavras seriam suficientes para descrever o quanto cada um dos passos que dei ao longo desses 13 anos juntos não seriam possíveis sem você ao meu lado. Você me inspira como profissional, filho, amigo, marido, pai e ser humano. Obrigada por me escolher como lar.

À minha filha, talvez grande responsável por esse passo ter sido, finalmente, dado. Por me fazer querer ser melhor a cada dia e por ter reacendido em mim a chama pela educação. Minha vida, te amo! Mais que tudo, mais que a vida, mais que o mundo!

Aos meus sogros, em especial minha sogra, que foi o maior sorriso que recebi ao descobrir a aprovação, e que sempre segurou minhas pontas ao longo dessa caminhada, extensivo à Vovó Lelinha, Du, Tamarinha e Pipe, minha inspiração e também razão.

Às famílias Sarmiento, Macedo, Signorelli, Gonçalves, da Silva Araújo e Pônzio,

hoje meu grande núcleo familiar. À Alciele (Vitória e Gabi) que esteve ao nosso lado, fazendo com que ausências fossem menos doloridas, sem você eu não teria feito nada.

À minha querida orientadora Camilla, que aceitou o desafio de orientar uma aluna há muito formada e sem experiência em pesquisa. Que me abraçou nessa caminhada mesmo sabendo que tantos outros poderiam trilhar esse caminho com mais facilidade, ainda assim, me escolheu. Por ensinar detalhes grandiosos sobre pesquisa, docência, escrita, convivência, trabalho em equipe, mas especialmente por tantas vezes abdicar de estar com os seus para ensinar. Espero que saiba o quanto de você agora vive em mim.

Serei eternamente grata à Gabi, que por generosidade me apresentou e foi referência para Camilla. Você, que esteve ao meu lado nessa caminhada tão importante, e tantas vezes foi companhia, risada, ombro e acima de tudo exemplo, minha gratidão. Ao Sávio, meu doce amigo, eterno parceiro. Nelly, te extraño tanto mi amiga. Gabi(zinha) e Tamarinha, minha primeira experiência de trabalho conjunto com alunos na graduação, sempre tão competentes e solícitas. Aos meus amigos Carol, João, Rôger. À Anahi, que com seu abraço acalmou tantas inseguranças e ao Dan, que se tornou meu fiel amigo, parceiro, ser humano ímpar e cérebro incrível, nada nesse trabalho existiria sem vocês.

Agradeço a Universidade Federal de Uberlândia, bem como o Programa de pós-graduação e a Faculdade de Odontologia por todas oportunidades que tive e permaneço tendo aqui em 8 anos de formação.

À CAPES pelo apoio financeiro a esta pesquisa.

Aos professores do programa de Pós-Graduação em Odontologia, que me abraçaram nesse caminho de volta e foram tão generosos nessa formação. À Lais e Brenda, que sempre me ajudaram prontamente.

Aos meus amigos, que independente do momento sempre estiveram ao meu lado com uma palavra de incentivo, um abraço e alguns puxões de orelha, Giovana, Garvil, Renata, Luiz Amui, Renata Georjutti, Rodrigo, Cristiane Cruz, Ana Paula Endo, Maria Silvia, Cristiane Caram, Anderson, Máira e outros tantos que mesmo sem perceber foram o estímulo necessário para continuar mais um dia.

Aos amigos que fiz no mestrado. Aos alunos que me inspiraram e à UNITRI que me permitiu e permite exercer a docência como sonho e acredito.

Minha eterna gratidão.

EPÍGRAFE

“A maior recompensa para o trabalho do homem não é o que ele ganha com isso, mas o que ele se torna com isso.”

(John Ruskin)

SUMÁRIO

Resumo	1
Palavras-chave	2
Abstract	3
Keywords	4
1. Introdução e referencial teórico	5
2. Capítulo 1	7
Title page	8
Abstract	10
Introduction	12
Methods.	14
Results	17
Discussion	18
Conclusion	28
References	29
Tables	35
Figures	44
3. Capítulo 2	46
Title page	47
Abstract	49
Introduction	50
Case Report	51
Discussion	54
Conclusion	56
Figures	57
Tables	59
References	61
4. Referencias	63

RESUMO

Introdução: Recentemente emergiu na endodontia um novo campo de estudo denominado medicina endodôntica, onde se avaliam os possíveis impactos sistêmicos das infecções de origem endodôntica, assim como os impactos de doenças sistêmicas, como doença renal em estágio final, no desenvolvimento e cicatrização das periodontites apicais (PA) de origem endodôntica. Dentro deste contexto tem-se estudado mediadores relacionados ao estresse oxidativo tanto localmente, no sítio da lesão, como sistemicamente, utilizando sangue, saliva, e fluido crevicular gengival. O desequilíbrio entre compostos oxidantes e antioxidantes leva ao estresse oxidativo. O estresse oxidativo tem sido relacionado à patogênese da PA, assim como a presença dessa patologia tem sido relacionada ao aumento do estresse oxidativo sistêmico com possível impacto em outras desordens inflamatórias. Como resultado, o número de publicações na área tem crescido, porém, os mediadores avaliados, os tipos de amostras utilizadas, os métodos de coleta e análise têm sido muito variáveis. Diante disso, este estudo teve como **Objetivos:** 1) mapear os métodos mais comumente usados para obtenção de amostras e análise dos níveis de espécies reativas de oxigênio na periodontite apical; 2) Relatar um caso de glomerulonefrite pós-estreptocócica cujo fator causal foi uma infecção endodôntica. **Métodos:** 1) a metodologia utilizada no estudo 1 seguiu a PRISMA Extension for Scoping Reviews e registrada no Open Science Framework ([Blinding]). Uma busca sistematizada foi realizada nas bases de dados eletrônicas MEDLINE (através do PubMed), Embase, Scopus, Web of Science, LILACS, SciELO, OATD e DANS Easy até 23 de janeiro de 2023. Os critérios de elegibilidade foram baseados em estudos clínicos, independentemente do desenho. Uma análise bibliométrica também foi realizada para avaliar a ocorrência de palavras-chave e periódicos com o software VOSViewer. 2) o estudo 2 relata o caso de um paciente adulto cuja história clínica, exames laboratoriais e laudo da biopsia levaram o médico responsável a contactar o cirurgião dentista a fim de buscar provável infecção oral, tendo o paciente apresentado dente 26 necrosado, sem doença periodontal subjacente, cáries ou outros tratamentos endodônticos. Foi indicado tratamento endodôntico do referido dente. **Resultados:** 1) O compilado de resultados da revisão de escopo mostra um total de 18 estudos foram incluídos. Os ensaios clínicos foram o desenho de estudo mais prevalente avaliado por esta revisão, seguido por estudos observacionais. Entre todos os estudos selecionados, lesões periapicais via cirurgias periapicais ou extrações dentárias

foram as amostras mais comumente coletadas. Apenas um estudo avaliou saliva e outro fluido crevicular gengival. Vinte e oito diferentes tipos de análise de estresse oxidativo foram identificados, sendo a sintase do óxido nítrico induzível avaliada por imuno-histoquímica a mais prevalente. Na análise bibliométrica, as 3 palavras-chave mais frequentes foram “periodontite apical”, “stress oxidativo”, e “óxido nítrico sintase induzível”. A maioria dos estudos incluídos foi publicada no International Endodontic Journal. 2) Após a conclusão do caso clínico e acompanhamento de 2,5 anos não foi relatada recidiva da doença ou alterações nos exames de sangue e urina que indicassem recidiva da glomerulonefrite pós-estreptocócica. Conclusões: 1) Segundo a revisão de escopo podemos concluir que embora haja uma variedade de biomarcadores para avaliar estresse oxidativo, não é possível identificar moléculas específicas de espécies reativas de oxigênio ou nitrogênio, bem como antioxidantes que podem servir como biomarcadores candidatos para avaliar o status da PA e potenciais impactos sistêmicos. Estudos envolvendo métodos menos invasivos como saliva e fluido crevicular gengival são necessários. 2) A infecção endodôntica por necrose pulpar pode ser a causa da glomerulonefrite pós-estreptocócica, e o tratamento endodôntico pode ajudar na rápida remissão dos sintomas da doença, reduzindo as recidivas e restaurando a qualidade de vida do paciente.

Palavras-chave: medicina endodôntica, periodontite apical, stress oxidativo.

ABSTRACT

Introduction: Recently, a new field of study called endodontic medicine has emerged in endodontics, which evaluates the possible systemic impacts of endodontic infections as well as the impacts of systemic diseases, such as end-stage renal disease, on the development and healing of apical periodontitis (AP) of endodontic origin. Within this context, mediators related to oxidative stress have been studied both locally, at the site of the lesion, and systemically, using blood, saliva, and gingival crevicular fluid. The imbalance between oxidant and antioxidant compounds leads to oxidative stress. Oxidative stress has been related to the pathogenesis of AP, and the presence of this pathology has been associated with increased systemic oxidative stress, with a possible impact on other inflammatory disorders. As a result, the number of publications in this area has increased, but the evaluated mediators, types of samples used, and collection and analysis methods have been highly variable. Therefore, this study aimed to 1) map the most commonly used methods for obtaining samples and analyzing reactive oxygen species levels in chronic apical periodontitis; 2) report a case of post-streptococcal glomerulonephritis whose causal factor was an endodontic infection.

Methods 1) The methodology used in study 1 followed the PRISMA Extension for Scoping Reviews and was registered in the Open Science Framework ([Blinding]). A systematic search was conducted in the electronic databases MEDLINE (via PubMed), Embase, Scopus, Web of Science, LILACS, SciELO, OATD, and DANS Easy up to January 23, 2023. Eligibility criteria were based on clinical studies, regardless of the design. A bibliometric analysis was also performed to evaluate the occurrence of keywords and journals using VOSViewer software. 2) Study 2 reports the case of an adult patient whose clinical history, laboratory tests, and biopsy report led the attending physician to contact the dentist to investigate a possible oral infection, as the patient presented with necrotic tooth 26 without underlying periodontal disease, caries, or other endodontic treatments. Endodontic treatment of the affected tooth was indicated.

Results: 1) The compilation of results from the scoping review shows a total of 18 studies were included. Clinical trials were the most prevalent study design evaluated in this review, followed by observational studies. Among all selected studies, periapical lesions via periapical surgeries or tooth extractions were the most collected samples. Only one study evaluated saliva, and another evaluated gingival crevicular fluid. Twenty-eight different types of oxidative stress analysis were identified, with inducible nitric oxide synthase evaluated by immunohistochemistry being the most prevalent. In the bibliometric analysis, the three most frequent keywords were "apical periodontitis," "oxidative stress," and "inducible nitric oxide synthase." The majority of included studies were published in

the International Endodontic Journal. 2) After the conclusion of the clinical case and a 2.5-year follow-up, no disease recurrence or changes in blood and urine tests indicating post-streptococcal glomerulonephritis recurrence were reported. Conclusions: 1) According to the scoping review, we can conclude that although there is a variety of biomarkers to evaluate oxidative stress, it is not possible to identify specific reactive nitrogen species or reactive oxygen species molecules, as well as antioxidants that can serve as candidate biomarkers to assess the status of AP and potential systemic impacts. Studies involving less invasive methods such as saliva and gingival crevicular fluid are needed. 2) Endodontic infection due to pulp necrosis can be the cause of post-streptococcal glomerulonephritis, and endodontic treatment can aid in the rapid remission of disease symptoms, reducing relapses and restoring the patient's quality of life.

Keywords: endodontic medicine, apical periodontitis, oxidative stress.

INTRODUÇÃO E REFERENCIAL TEÓRICO

A periodontite apical (PA) é caracterizada como um processo inflamatório ao redor do ápice radicular, causada por infecção microbiana no espaço pulpar, e pode ser apontada como uma resposta tecidual à agressão microbiana, com formação de lesão osteolítica (Rôcas *et al.* 2014).

Quando frente a uma lesão tecidual ou infecção por patógenos, o sistema imune é capaz de desenvolver uma complexa estratégia de defesa. O sistema inato, é geneticamente programado para identificar danos celulares e invasão de microrganismos. Macrófagos, células dendríticas, neutrófilos, basófilos, eosinófilos, mastócitos e células natural killer fazem parte desse complexo grupamento celular (Viola, *et al.* 2019).

Os macrófagos são células altamente especializadas que podem identificar, englobar e destruir patógenos e células apoptóticas rapidamente. Devido ao processo chamado de “polarização”, são capazes de responder aos mais diversos estímulos do microambiente tecidual, possuindo alta plasticidade. Podem adotar um perfil inflamatório imediato, visando controlar e reverter a infecção, e em seguida adquirir perfil anti-inflamatório enquanto permite a cicatrização dos danos teciduais (Viola, *et al.* 2019).

Um dos mecanismos comumente adotados por células do sistema inato para combater agressões envolve a produção de Espécies Reativas de Oxigênio (ERO), importantes sinalizadores celulares, capazes de modular alterações desde o retorno à homeostase, até a apoptose (Hernández-Ríos, *et al.* 2017). Apesar de determinante fator no sistema de defesa, um distúrbio do balanço oxidativo pode resultar em lesão tecidual (Nathan *et al.* 2013).

Um aumento na prevalência de periodontite apical em dentes tratados e não tratados endodonticamente em adultos, entre os anos de 2012 e 2020, foi demonstrada em estudo recentemente publicado (Jakovljevic, *et al.* 2020). Também tem sido observado um aumento do estresse oxidativo local e sistêmico em pacientes que apresentam PAC (Inchingolo *et al.* 2013,

Hernández-Ríos et al. 2017, Vengerfeldt et al. 2017).

Estudos recentes demonstram a correlação entre a presença de doença periapical e aumento dos níveis de estresse oxidativo local e sistêmico, porém, devido à diversidade de metodologias, torna-se desafiador constatar o real impacto da doença endodôntica sobre esses parâmetros, bem como propor metodologias futuras para análise de desordem redox e tratamentos para seu reequilíbrio (Georgiou et al. 2021).

O estresse oxidativo está envolvido no mecanismo de aparecimento de lesões periapicais, mas a degradação celular causada por oxidação é um mecanismo relevante e fortemente envolvido na patogênese das mais diversas doenças crônicas inflamatórias, incluindo diabetes mellitus, doença cardiovascular, aterosclerose, artrite e câncer (Akalın *et al.*, 2007 e 2008; Nunes *et al.*, 2012). Recentemente, correlacionou-se um maior número de tratamentos endodônticos e PAC à presença de doença renal crônica em estágio final, embora não se saiba definir exatamente os fatores causais (Khalighinejad et al. 2017). No entanto pouco se sabe sobre o envolvimento das PA no desenvolvimento das glomerulonefrites, especialmente as de origem microbiana. A glomerulonefrite pós-estreptocócica (GNPS) é uma doença renal aguda, que pode ser causada por bactérias, vírus, parasitas e fungos, mas é mais comumente relatada como bacteriana associada ao grupo de estreptococos β -hemolítico tipo A, e tem sido relacionada a infecções da pele e do trato respiratório (Rodriguez-Iturbe & Haas, 2016B; Satoskar et al., 2020).

Considerando o impacto sistêmico que as PA podem exercer e as lacunas ainda presentes na literatura, o objetivo do presente trabalho é apresentar uma revisão de escopo sobre métodos de análises, amostras e marcadores de estresse oxidativo locais e sistêmicos em pacientes com PA e relatar um caso de glomerulonefrite pós streptococcica com provável origem endodôntica.

Screening oxidative stress analyses in patients with apical periodontitis: a scoping review

Macedo Signorelli NS, Rende SGS, Ferraz DC, Paranhos LR, Moura

CCG

Type of article: Original

Title of the article: Screening oxidative stress analyses in patients with apical periodontitis: a scoping review

Keywords: Reactive Oxygen Species, Oxidative Stress, Apical Periodontitis

Author information:

1. Nara Sarmento Macedo Signorelli - MS Student
2. Sávio Gabriel Silva Rende – Dentist, graduate
3. Danilo Cassiano Ferraz- PhD Student
4. Luiz Renato Paranhos - Professor, PhD
5. Camilla Christian Gomes Moura - Professor, PhD

Department(s), institution(s), and email address

1. Post-graduation Program in Dentistry, School of Dentistry, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil. profnarasignorelli@gmail.com
<https://orcid.org/0000-0002-8460-7795>
2. Post-graduation Program in Patients with Special Needs, School of Medicine, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil. rendesavio@gmail.com
<https://orcid.org/0000-0001-5907-7852>
3. Post-graduation Program in Dentistry, School of Dentistry, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil. ferrazd01@gmail.com
<https://orcid.org/0000-0001-9102-4320>

4. Department of Preventive and Social Dentistry, School of Dentistry, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil. paranhos.lrp@gmail.com <https://orcid.org/0000-0002-7599-0120>
5. Department of Endodontics and Dental Materials, School of Dentistry, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil. camillamoura@ufu.br <https://orcid.org/0000-0002-5653-8403>

Institution to which the work should be attributed

Department of Endodontic and Dental Materials, School of Dentistry, Federal University of Uberlândia, Campus Umuarama, Av. Pará, 1720, Bloco 2G. camillamoura@ufu.br

Corresponding author

Prof. Dr. Camilla Christian Gomes Moura

Department of Endodontic and Dental Materials, School of Dentistry, Federal University of Uberlândia, Campus Umuarama, Av. Pará, 1720, Bloco 2G ZIP code: 38405-320, Uberlândia, MG, Brazil. camillamoura@ufu.br

Sources of support

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES) - Finance Code 001. We are also thankful for the support of Conselho Nacional de Desenvolvimento Científico e Tecnológico - Brazil (CNPq) and Fundação de Amparo à Pesquisa do Estado de Minas Gerais – Brazil (FAPEMIG).

Disclosure statement

The authors declare that there is no conflict of interest.

ABSTRACT

Background: The imbalance between oxidant and antioxidant compounds leads to oxidative stress (OS). OS has been related to the pathogenesis of apical periodontitis (AP), as the presence of this pathology has been related to increased systemic OS with possible impact in other inflammatory disorders. As a result, the number of publications in the area has grown, however, the mediators' evaluated, the types of samples used, collection and analysis methods have been highly variable.

Objectives: The aim of this study is to map the most commonly used methods for obtaining samples and analyzing reactive oxygen species levels in chronic apical periodontitis.

Method: This review was conducted following the PRISMA Extension for Scoping Reviews and registered in Open Science Framework ([Blinding]). A systematic search was carried out in electronic databases MEDLINE (through PubMed), Embase, Scopus, Web of Science, LILACS, SciElo, OATD and DANS Easy up to January 23, 2023. Eligibility criteria were based on clinical studies, regardless of the design study. A bibliometric analysis was also conducted to assess authorship, the occurrence of keywords, and journals with VOSViewer software.

Results: A total of 18 studies were included. Clinical trials were the most prevalent study design assessed by this review, followed by observational studies. Among all selected studies, periapical surgeries or tooth extractions were the most common sample collected. Only one study evaluated saliva, and one gingival crevicular fluid (GCF). Twenty-eight different types of oxidative stress analysis were identified, being inducible nitric oxide synthase evaluated by immunohistochemistry the most prevalent. In bibliometric

analysis, the top 3 most frequent keywords were Humans, Adults, and Female. The majority of included studies were published in Journal of Endodontics and International Endodontic Journal.

Conclusions: The use of a variety of biomarkers to assess OS does not allow for the identification of specific RNS or ROS molecule, as well as antioxidant that can serve as candidate biomarkers for assessing AP status and potential systemic impacts. Studies enrolling less invasive methods as saliva and GCF are necessary.

Keywords: Reactive Oxygen Species, Oxidative Stress, Apical Periodontitis

INTRODUCTION

Apical periodontitis (AP) with endodontic origin refers to inflammation of the apical periodontium that is both acute and chronic and caused by microorganisms inside the root canal system (Dezerega et al., 2012; Braz-Silva et al., 2019; Barcelos et al., 2020; Georgiou et al., 2023). This inflammation is a result of immune-inflammatory reactions triggered by endodontic infection, which is mainly caused by anaerobic bacteria (Nair, 2004; Hernandez-Rios, 2017). These reactions lead to the recruitment of immune cells, such as neutrophils, macrophages, T cells, and mast cells, and the release of cytokines (Braz-Silva et al., 2019; van der Wall, 2023), chemokines (Braz-Silva et al., 2019; Hasegawa et al., 2021; van der Wall, 2023), along with the generation of reactive species (RS) (Barcelos et al., 2020; Georgiu et al., 2021).

RS, produced by phagocytic cells, are small internal signaling molecules that have garnered significant research interest, as their levels correlate with changes in the local immune-inflammatory environment of AP and systemic changes (Georgiou et al., 2021; Barcelos et al., 2020; Georgiou et al., 2023). RS are classified based on the type of reactive atom they contain into three categories: reactive oxygen species (ROS), reactive sulfur species (RSS), and reactive nitrogen species (RNS) (Nathan and Cunningham-Busseet, 2013; Sies and Jones, 2020; Sies et al., 2022). These species play a role in fighting microorganisms and controlling the spread of infection (Braz-Silva et al., 2019; Barcelos et al., 2020). In particular, their activity can result in periapical bone tissue destruction, which is a characteristic of apical periodontitis (Galler et al., 2021; Dezerega et al., 2012; Braz-Silva et al., 2019; Barcelos et al., 2020; Georgiou et al., 2023). Among the RS, ROS have been the primary focus in studies that have examined their presence both locally (Kabashima et al. 1998; Dezerega et al. 2012) and systemically in blood (Minczykowski et al. 2001; Cotti et al. 2015; Inchingolo et al. 2014; Gomes et al. 2017),

saliva (Vengerfeldt et al. 2017; Konoplya et al. 2018), and gingival crevicular fluid (GCF) (Dezerega et al. 2012) in AP.

The term ROS refers to a group of molecules formed from oxygen through oxidation and reduction reactions (Redox) or electronic excitation and includes both non-radical and free-radical species (Nathan and Cunningham-Busseet, 2013; Sies and Jones, 2020; Barcelos et al., 2020; Sies et al., 2022). Although ROS are often remembered for their pathogenic mechanisms and potentially destructive effects on microorganisms, these molecules possess dual roles, acting both in the cell signaling processes essential for the tissue homeostasis, and in the destructive processes when their levels increase (Georgiou et al. 2021). To counteract the harmful effects of excessive ROS, cells have developed various antioxidant mechanisms, which include enzymes such as superoxide dismutase (SOD), glutathione (GSH), peroxidase (GPx ou GSH-Px), peroxiredoxins (GR ou GSH-Rd), catalase (Cat), and others (Schmidt et al., 2015, Georgiou et al. 2021).

Excessive levels of ROS can be toxic and cause damage to proteins, lipids, and DNA (Nathan and Cunningham-Busseet, 2013; Sies and Jones, 2022) leading to tissue damage known as oxidative stress (OS). Several animals and human clinical studies have evaluated the relationship between AP and an increase in OS both local and systemic levels (Hernandez-Rios et al. 2017; Georgiou et al. 2021). However, the diagnosis of AP (symptomatic or asymptomatic), mediators being evaluated, the types of samples used, and the collection and analysis methods have been highly variable and have led to results that are difficult to compare (Hernandez-Rioz et al. 2017, Georgiou et al. 2021). Recently, a systematic review examined local and systemic traces of ROS in endodontic pathologies (Georgiou et al., 2021), to determine if different clinical conditions or histopathological specimens of AP results in a different magnitude of ROS levels. However, the obtained findings are quite broad due to the wide range of methodologies used and different

endodontic pathologies included. In fact, is still challenging to determine which parameters should be evaluated in future clinical studies. Therefore, the aim of this study is to map the most commonly used biomarkers, samples and methods for analyzing OS in AP.

METHODS

This scoping review was drafted using the guidelines of the JBI Manual for Evidence Synthesis (Aromataris & Munn; 2020) and reported following PRISMA Extension for Scoping Reviews (PRISMA-ScR) (Trico et al., 2016). The final protocol was registered prospectively with the Open Science Framework on January 17th of 2023 (<https://osf.io/d5u76>).

Study design and eligibility criteria

This review was supported by a guiding question according to PCC strategy, in which Population were patients with apical periodontitis, the Concept was evaluating oxidative/nitrosative stress and different methodologies for sample collection and analysis of reactive species and the Context, were general population, resulting in the question: What collecting, biomarkers and analyzing sample models are used to assess oxidative stress in patients with apical periodontitis?

Inclusion criteria considered experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies were included. Descriptive observational study designs

including case series, individual case reports were also considered. Patients should have diagnosis of apical periodontitis, and presence of periapical lesion confirmed in radiographic image, with clinical confirmation of pulpal necrosis. The search had no restriction on publication year or language. The following exclusion criteria were used: literature reviews, book sections, congress abstracts, commentaries, opinion or hypothesis articles, editorial letters, studies with animals, and laboratory trials (bank of tissue, cell isolations). Studies involving the use of antibiotics and anti-inflammatories for less than 3 months or periodontal disease or any other systemic disease that was purposely not included for evaluation, studies involving bank of histological slides, using apical periodontitis as a model of inflammatory disease or those who did not have a clear description of the individuals included in their methodology were excluded.

Sources of information, search and study selection

The primary study sources chosen for this review were MEDLINE (via PubMed), LILACS, SciELO, EMBASE, Scopus, and Web of Science. Open Access Theses and Dissertations (OATD) and Data Archiving and Networked Services (DANS) database were used to partially capture “grey literature”.

All descriptors were defined through keywords, MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors), and Emtree (Emtree Subject Headings) databases. Several combinations between descriptors were made by Boolean operators “AND” and “OR”, accordingly syntax rules of each database (Table 1).

Studies were obtained from each database and imported to EndNote X9 (Thomson Reuters, Toronto, Canada) software. Duplicates were automatically excluded and those not detected by the software were manually deleted. Duplicates from grey literature were analyzed manually by Microsoft Word™ 2019 (Microsoft™ Ltd., Washington, USA).

Studies then were exported to Rayyan QCRI (Qatar Computing Research Institute, Doha, Qatar) (Ouzzani, et al., 2016), in which a selection study was performed. All study selection phases were performed by two reviewers (NSMS and SGSR) independently. Titles and abstracts were screened by the same two reviewers. Studies out of scope and those that did not meet the eligibility criteria were eliminated. The results in which the titles were in accordance with the objectives of this review but did not have abstracts available were fully assessed. Any conflict of selection was solved by consulting a third reviewer (DCF) for the final decision. The citation search assessment was made by reading references of eligible records. Eligibility criteria was applied equally as for studies obtained through electronic searches databases.

Data extraction and synthesis

Following PRISMA-ScR recommendation (Trico et al., 2016.), all data were obtained independently by the two reviewers (NSMS and SGSR). After the initial collection, the third reviewer (DCF) double-checked all retrieved data to avoid errors. The following data were collected: identification of study (author, year, country), sample characteristics (population recruitment, sample size), study design, inclusion and exclusion criteria, systemic health conditions (Table 2), and sample acquire, intervention, types of oxidative stress analyzed, evaluation method and oxidative stress outcome (Table 3). No critical appraisal of individual sources of evidence was performed since the aim of this review is to map different oxidative stress analyses in patients with CAP.

RESULTS

Study selection

A total of 4.886 potentially relevant records were identified from all electronic searches.

After duplicate removal, 2,553 records were screened by title and abstract. Eligibility criteria were applied, and 13 studies were included, and 5 studies were identified by citation search. A total of 18 studies were included in this review. All details of the study selection were summarized in Figure 1.

Bibliometric analyses

Density visualization indicated that “apical periodontitis”, “oxidative stress”, and “inducible nitric oxide synthase” were the most popular keywords used by authors. There was a high association between OS and systemic diseases in AP (Figure 2).

From 18 articles included in this scoping review, were identified 12 journals, of which “International Endodontic Journal” acquire the top rank with 4 published articles (Figure S1).

Characteristics of included studies

The included studies were reported from different countries across Asia, Europe, Eurasia, North America and South America. The studies were comprised between 1993–2022 with higher prevalence in to last two decades. The population number varied between 10 and 136 participants across selected studies. The most prevalent design study was clinical trials (Marton et al., 1993; Kabashima et al., 1998; Takeichi et.al., 1998; Takeichi et.al., 1999; Hama et al., 2006; Hama et al., 2007; Inchingolo et al., 2014; Vengerfeldt et al., 2017; Bains et al., 2021) followed by observational studies (Shimauchi et al.,2001; Cotti, et al., 2015; Gomes et al., 2017; Jakovljevic et al., 2018; Kudo et al., 2018; Loureiro et al., 2021; Loureiro et al., 2022; Loureiro et al., 2023). From all studies, only three approached systemic diseases as a variable (depression, Epstein–Barr virus and diabetes mellitus) (Gomes et al., 2017; Jakovljevic et al., 2018; Loureiro et al., 2022). A summary

of the main characteristics of the included studies were described in Table 2.

Synthesis of results

Results were summarized in Table 3. In general, the acquisition of samples was related to the intervention. The apical lesion (AL) samples were collected chiefly in periapical surgeries (Marton et al., 1993; Kabashima et al., 1998; Takeichi et al. 1998, Takeichi et al. 1999; Hama et al., 2006; Hama et al., 2007; Kudo et al., 2018) or tooth extractions (Dezerega et al., 2012). The effect of endodontic treatment at different OS markers was also evaluated (Dezerega et al., 2012; Bains et al., 2021). It was identified twenty-eight different types of OS analysis. The most prevalent OS type was the inducible nitric oxide synthase (iNOS) enzyme identification (Kabashima et al., 1998; Takeichi et al. 1998, Takeichi et al. 1999; Shimauchi et al., 2001; Hama et al., 2006; Hama et al., 2007). In included studies in this review CAPs groups showed higher (or positive) levels of OS when compared to healthy groups (Marton et al., 1993; Kabashima et al., 1998; Dezerega et al., 2012; Inchingolo et al., 2014; Cotti et al., 2015; Gomes et al., 2017; Vengerfeldt et al., 2017; Jakovljevic et al., 2018; Kudo et al., 2018), excepted for Bains et al (2021), a before and after study, that presented equal levels of GSH before and after endodontic intervention.

DISCUSSION

The present scoping review was conducted to map the literature regarding the most used methods for obtaining samples and analyzing OS in participants with AP with presence of apical radiolucency. Although two previous reviews have addressed the topic of OS and AP (Hernandez-Rios et al. 2017; Georgiou et al. 2021), the present scoping review has unique characteristics that differentiates it from the previous reviews. The review

published by Hernández-Ríos et al. (2017) was the first to explore the relationship between local and systemic OS and its association with AP, as well as the potential connections between OS and other conditions, such as atherosclerosis. However, this review was published over 5 years back and may not meet the current methodological standards expected in scoping reviews. In contrast, the systematic review published by Georgiou et al. (2021) is recent and well structured, the objectives and methodologies employed in the two types of reviews are different.

Furthermore, the systematic review conducted by Georgiou et al. (2021) included a wide range of endodontic pathologies, such as pulpitis, abscesses, and symptomatic and asymptomatic apical periodontitis (with and without apical lesions), which have different courses of formation and evolution (Gomes et al. 2013; Braz-Silva et al. 2019).

OS mechanism and primary markers

The increased production of oxidant components leads to a disruption in the redox balance and a simultaneous decrease in the level of antioxidants, resulting in the development of a pro-oxidant state, known as OS (Nathan and Cunningham-Busseet, 2013; Sies and Jones, 2020; Sies et al., 2022). The studies included in this scoping review encompass a variety of OS markers, including pro-oxidants, such as ROS and RNS, and antioxidants, such as SOD enzymes, GSH, GSH-Px, and GSH-Rd (Marton et al. 1993; Shetty and Kumari, 2012; Jakovljevic et al. 2018; Bains et al. 2021; Loureiro et al. 2021, Loureiro et al. 2022, Loureiro et al. 2023).

Nitric oxide synthase (NOS), which includes inducible NOS (iNOS) as one of its isoforms, was the most extensively evaluated form of RNS in CAPs, observed in a total of seven studies (Kabashima et al. 1998; Takeichi et al. 1998; Takeichi et al. 1999; Hama et al. 2006; Hama et al. 2008; Cassanta et al. 2017). This enzyme is produced by

macrophages, neutrophils, lymphocytes, and fibroblasts stimulated by bacterial lipopolysaccharides (LPS) or induced by other pro-inflammatory cytokines, such as IL-1 β , IL-6, TNF α , and interferon- γ (IFN- γ) (Takeichi et al. 1998; Canton et al. 2021). The iNOS generates nitric oxide (NO) through the cleavage of arginine by arginase, which mediates periapical tissue destruction and may causes chronic inflammation and expansion of the lesion (Takeichi et al. 1998; Suzuki et al. 2002, Silva et al. 2001). Nitrite is the stable end product of NO oxidation, and its concentration was determined from the sample collected from the canal (Shimauchi et al. 2001), and plasma (Gomes et al. 2017). The presence of iNOS and NO in CAPs appears to modulate the degree of inflammation and osteoclastic activity (Kabashima et al. 1998).

ROS induces lipid peroxidation, which can lead to disruption of the cell integrity (Girotti, 1998). Among the numerous lipid peroxidation markers used to monitor this process, malondialdehyde (MDA) was quantified in samples obtained from ALs (Marton et al. 1993). Additionally, plasma quantification of lipid hydroperoxides (LOOH) had also been used as another marker to assess lipid peroxidation (Gomes et al. 2017). Myeloperoxidase (MPO) is another enzyme involved in the initiation of lipid peroxidation (Vengerfeldt et al. 2017). Additionally, H₂O₂ can be used to generate other oxidants, such as HOCl, which are used in the defense against pathogens and for degradation of the extracellular matrix (Sies and Jones, 2020). Three studies included in this review evaluated MPO levels (; Vengerfeldt et al. 2017; Loureiro et al. 2021, Loureiro et al. 2022), and one of them assessed samples obtained from the root canal and saliva, confirming high local and systemic levels of MPO in CAP (Vengerfeldt et al. 2017). In the same study, 8-EPI was also evaluated, which constitutes a stable end product of ROS-mediated prostanoid oxidation and is also associated with lipid peroxidation and DNA damage. Protein modifications induced by ROS, such as oxidation, were assessed by measuring advanced

oxidation protein products (AOPP) and protein-SH oxidative modifications, which were quantified in the plasma of individuals diagnosed with depression and AP (Gomes et al. *et al.* 2017). Notably, oxidative damage also affects DNA, similar to its impact on lipids and proteins. One of the most common biomarkers of DNA oxidative damage is 8-hydroxy-2'-deoxyguanosine (8-OHdG), which was evaluated in two studies investigating the expression of 8-OHdG in samples obtained from apicectomy (Kudo et al. 2018, Jakovljevic et al. 2018).

ROS are generated by various sources, with H_2O_2 and O_2^- being the primary species generated. H_2O_2 exhibits pleiotropic activities, simultaneously affecting several cellular functions. However, when produced at supraphysiological levels, it causes damage to biomolecules and can lead to cell death (Sies and Jones, 2020). The products of cellular damage generated by H_2O_2 can function as secondary oxidative signals. When oxidative stress occurs, the non-physiological generation of H_2O_2 can interfere with redox signaling. In the present review, no study directly evaluated the levels of H_2O_2 and O_2^- . Although Minczykowski et al. (2001) had performed a direct evaluation of H_2O_2 and O_2^- , using polymorphonuclear cell samples obtained from the blood of individuals with CAP before and after tooth extraction, this study was not included because it isolated the cells for analysis, thus constituting a laboratory study and not a clinical one. Four studies performed indirect measurements which were referred to as total peroxide concentration (TPX) (Vengerfeldt et al. 2017), ROS dosage (Cotti et al. 2015), or total oxidant status (TOS) (Dezerega et al. 2012, Inchingolo et al. 2014). Moreover, different tests were employed by these studies, such as OxyStat colorimetric kit (Biomedica, Wien, Austria), free oxygen radical test (FORT), or d-ROMs test kit (Diacrom International, Grosseto, Italy).

Several antioxidants, primarily enzymatic, were included in this scoping review, such as

SOD, and glutathione peroxidase (GSH-Px) (Gulcin, 2020; Munteanu and Apetrei 2021). SODs are the first and main protective barrier against OS and have been evaluated by one study included in the present review (Marton et al. 1993). These enzymes catalyze the dismutation of O_2^- into H_2O_2 . Following the O_2^- dismutation reaction, the H_2O_2 is metabolized by catalase or GSH-Px. GSH is considered one of the “master antioxidants” because it prevents the impairment of essential cellular components by ROS and functions as a cofactor for other antioxidants (Bains et al. 2021). The metabolism of H_2O_2 into H_2O and glutathione disulfide (GSSG) by GSH-Px requires the reduced form of GSH as a cofactor. Although the three forms of glutathione, GSH-Px (Marton et al. 1993), GSSG (Jakovljevic et al. 2018), and GSH (Bains et al. 2021) were measured in the studies, the type of sample used varied across the experiments. Peroxiredoxins, enzymes responsible for catalyzing the removal of excess H_2O_2 , also play a role in controlling H_2O_2 levels. Peroxiredoxins 1 and 2, along with their isoforms were evaluated in three studies using nano liquid chromatography (Loureiro et al. 2021, 2022, 2023).

Various methods are available to measure the activity of the antioxidants, which are based on the specific chemical reactions involved (Munteanu and Apetrei, 2021). The tests based on the transfer of the hydrogen atom from antioxidants to free radicals include the total peroxyl radical trapping antioxidant parameter (TRAP), which was used by Gomes et al. (2017). Three studies included in this review assessed antioxidant capacity using commercial kits measuring the inhibition of free radicals formation by the antioxidants from the samples, named total antioxidant status (TAS) (Dezerega et al. 2012; Inchingolo et al. 2014) or total antioxidant capacity (TAC) (Vengerfeldt et al. 2017).

Despite the evaluation of a wide variety of components and predominant focus on iNOS evaluations, recent studies published in the last five years assessed at least one marker related to oxidant capacity and one related to antioxidant capacity. This is because an

imbalance in the pro-oxidant-antioxidant compounds, in favor of the former, had been responsible for events, such as a decrease in osteoblast differentiation, an increase in RANKL-mediated osteoclast activation, elevated activity of metalloproteinases 1 and 9, and enhanced pro-inflammatory cytokine secretion (Silva et al. 2011; Hernandez-Rios et al. 2017; Barcelos et al. 2020; Francisconi et al. 2023).

Sample collection and methods of analysis

Most of the proposed methodologies (n=14) involved assessment of local biomarkers. Among the local analyses, seven studies obtained granulomatous tissues from the apical region through biopsy or apicectomy (Marton et al., 1993; Kabashima et al., 1998; Takeichi et al. 1998, Takeichi et al. 1999; Hama et al. 2006; Hama et al. 2007; Kudo et al. 2018), and one study obtained tissues after tooth extraction (Dezerega et al., 2012). These tissues were used for immunohistochemical and/or immunofluorescence analyses, enzyme-linked immunosorbent assay (ELISA), or various biochemical assays, including spectrometry (Munteanu & Apetei 2021). Although AL provides sufficient sample for assessing cellular and immunological characteristics, this methodology does not allow for the assessment of potential systemic repercussions. In the referred studies, the periodontal ligament or pulp tissue of a healthy tooth acts as a control, which constitutes a limitation, as biomarkers present at the site may vary depending on the type of immune response generated due to infection, potentially leading to differences in OS markers in healthy and diseased tissues.

Another interesting method of local sample collection involves obtaining it from the root canal in close proximity to the apex, referred to as periapical exudates (Takeichi et al., 1998), or paper points over the apex (Shimauchi et al., 2001; Loureiro et al., 2021; Loureiro et al., 2022; Loureiro et al., 2023). The collection of samples from the root canal

allows for the identification and quantification of human and microbial proteins. Sample collection using absorbent paper points is easy to perform and does not generate additional costs or steps in endodontic treatment. Additionally, this method is less invasive than other local collection methods, such as apicectomy. In contrast, obtaining a significant amount of sample for analysis using traditional biochemical and immunoenzymatic methods may be challenging in these samples. Recent studies have indicated the possibility of quantitative proteomic analysis using samples collected through absorbent paper cones positioned within the root canal (Loureiro et al. 2021, 2022, 2023). The application of proteomic analysis through mass spectrometry platform based on nanoflow liquid chromatograph in endodontic studies requires fewer samples for analysis and can evaluate different components simultaneously (Loureiro et al. 2020, Loureiro et al. 2021, Loureiro et al. 2023). This kind of proteomic analysis can be employed to various sample types, including saliva, GCF, and granulomatous tissues obtained from apicectomies. However, this method is limited by its cost, accessibility, and the need for specialized expertise (Grocholska et al. 2023).

The systemic impact of CAP was assessed in six studies, which utilized blood (Inchingolo et al., 2014; Cotti et al., 2015; Gomes et al., 2017; Bains et al. 2021), saliva (Vengerfeldt et al., 2017), or GCF (Dezerega et al., 2012) as samples. In studies using blood as a sample, variability exists in the use of plasma and blood serum (Forman et al., 2016). For collections involving blood samples, prompt removal of blood cells by centrifugation immediately after collection is crucial to avoid the production of hydrogen peroxide. In case of delayed extraction, the platelets present in the sample are capable of releasing inflammatory mediators, which can contribute to higher serum levels of OS markers. Other limitations associated with blood selection include the requirement for specialized personnel for proper collection, centrifugation, and immediate freezing to minimize

interference with the evaluated markers (Nunez et al., 2023). Despite this, several studies have used blood-derived biofluids, such as serum, plasma, and whole blood samples for quantification of OS. However, saliva has gained increasing prominence in studies of this nature (Şimşek et al., 2018; Chojnowska et al., 2023).

Saliva is a biofluid that serves as a reservoir of large amounts of molecules and may be potentially influenced by bacterial infections in the oral cavity, such as AP (Chojnowska et al., 2023), as well as the host's immune system response. It contains inorganic and organic species secretion products, such as lipids, proteins, metabolites, components of the microbiome, and abundant coding- and non-coding RNA species (Pfaffe et al., 2011; Chojnowska et al., 2018). Many of these molecules and salivary metabolites can be quantified using diverse techniques, such as immunoassays, colorimetric, enzymatic, chromatographic, magnetic resonance spectroscopy, mass spectrometry, and Fourier-transform infrared spectroscopy (Hyvärinen et al., 2023; Grocholska et al., 2023).

Despite the resemblance of the saliva molecular profile to blood, it offers advantageous simplifications as a diagnostic tool. The collection of saliva samples is noninvasive, requiring minimal expertise, and incurring low costs. Additionally, storage of saliva samples is simple and cost-effective, and frozen samples can be stored for an extended period of time (Pfaffe et al., 2011; Chojnowska et al., 2018; Hyvärinen et al. 2023). Furthermore, saliva remains stable for 24 h at room temperature or up to 7 days at 4 °C after collection. In addition, multiple samples may be collected at different times, allowing for repeated sampling (Chojnowska et al., 2018).

Although the study by Vengerfeldt et al. (2017) evaluated MPO and 8-EPI in saliva using ELISA, neither of these kits is specially designed for the diagnosis of salivary OS. The development of simplified kits specifically for the analysis of salivary OS in a dental setting is recommended. Additionally, the evaluation of salivary OS in CAP studies

requires methodological cross-validation by comparing saliva with other solid or blood samples, before considering saliva as the analyte of choice.

One of the studies included in this review (Dezerega et al., 2012) evaluated OS in GCF, which has been used for the diagnosis and monitoring of various periodontal diseases (Taylor & Preshaw, 2016; Majeed et al., 2016, Şimşek et al., 2018); however, GCF has also been investigated in APs in recent years (Nunez et al., 2023). GCF is a physiological serum transudate originating from the gingival plexus of blood vessels. It is produced and secreted into the gingival crevice between the tooth and epithelium, acting as a barrier against bacterial invasion (Khurshid et al., 2017). The various elements found in GCF include a mix of serum and locally produced proteins; soluble molecules such as antibodies, inflammatory mediators, cytokines, leucocytes, and enzymes; and organic/inorganic ions produced by periodontal cells and leukocytes (Subbarao et al., 2019). GCF offers several advantages, including easy, quick, and non-invasive collection that can be performed chairside. Additional studies are required to further investigate the utility of this biofluid for evaluating OS biomarkers in CAP.

Bibliometric analyses

The bibliometric analysis demonstrated that during the research period of 30 years, the most productive period was in the previous decade, with increased production in the last five years, indicating continuous research interests in this field. With regard to countries/regions unbalanced production was observed among countries. Japan led in the number of publications. Only five papers were published in Latin America, four of them specifically in Brazil, with close ties with other countries in the global cooperation network. The predominance of publications in endodontics-specific journals, such as JOE and IEJ, may be related to the authors' main area of interest, as well as to the impact factor

of these journals; however, publications were also found in journals enrolled in immunology as Immunology, and Oral Microbiology & Immunology, demonstrating that OS in AP is a topic that involves the integration of different disciplines. A total of five journals are not related to dentistry, promoting the integration and development of different subjects.

The analysis of co-occurrence keywords revealed a close relationship between OS and systemic diseases in AP, such as cardiovascular disease, Epstein-Barr virus, and diabetes mellitus. This finding is consistent with the upcoming association between PAC and systemic diseases (Ye, et al., 2023).

Limitations

The main limitation found in the development of the methodology of this review was the diagnosis of apical periodontitis and varied descriptions of these disease present in the literature. To minimize potential confounding, we choose clinical (necrosis) and radiographic (presence of apical radiolucency) characteristics to enable inclusion in the study. Papers that, despite citing clinical diagnoses, did not have radiographic characteristics or the opposite, were therefore excluded. Additionally, given the lack of risk of bias assessment or a process to establish certainty in the synthesised results, the results of our analyses should be interpreted judiciously and be viewed as indicative as opposed to confirmatory.

CONCLUSION

The use of a variety of biomarkers to assess OS does not allow for the identification of specific RNS or ROS molecule, as well as antioxidant that can serve as candidate biomarkers for assessing CAP status and potential systemic impacts. Among the

biomarkers evaluated for OS in CAPs, iNOS was the most frequently assessed with the predominant use of immunohistochemical analyses. The most commonly used on-site sample for evaluating OS in CAP was the AL itself, obtained through either tooth extraction or surgical removal of the granulomatous lesion. Although only few studies employed this approach, the sample obtained from absorbent paper points allows for an evaluation of OS during the execution of endodontic treatment, holding great potential for future local assessments.

REFERENCES:

1. Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available from <https://synthesismanual.jbi.global>
<https://doi.org/10.46658/JBIMES-20-01>
<https://doi.org/10.46658/JBIMES-20-01>
2. Bains, R, Tikku, AP, Chandra, A, Ali, W and Verma, P, 2021. Effect of Endodontic Treatment on Serum Glutathione (GSH) Levels in Patients with Chronic Apical Periodontitis: A Clinical Pilot Study. *Journal of Advanced Oral Research*, 12(1), pp.81-85. doi: <https://doi.org/10.1177/2320206820958239>
3. Barcelos RCS, Rosa HZ, Roversi K, Tibúrcio-Machado CDS, Inchaki PT, Burger ME, Bier CAS. Apical periodontitis induces changes on oxidative stress parameters and increases Na⁺/K⁺-ATPase activity in adult rats. *Arch Oral Biol*. 2020 Oct;118:104849. doi: 10.1016/j.archoralbio.2020.104849. Epub 2020 Aug 7. PMID: 32847752.
<https://doi.org/10.1016/j.archoralbio.2020.104849>
4. Braz-Silva PH, Bergamini ML, Mardegan AP, De Rosa CS, Hasseus B, Jonasson P. Inflammatory profile of chronic apical periodontitis: a literature review. *Acta Odontol Scand*. 2019 Apr;77(3):173-180. doi: 10.1080/00016357.2018.1521005. Epub 2018 Dec 26. PMID: 30585523.
<https://doi.org/10.1080/00016357.2018.1521005>
5. Canton M, Sanchez-Rodriguez R, Spera I, Venegas FC, Favia M, Viola A and Castegna A (2021) Reactive Oxygen Species in Macrophages: Sources and Targets. *Front. Immunol*. 12:734229. doi: 10.3389/fimmu.2021.734229
<https://doi.org/10.3389/fimmu.2021.734229>
6. Cassanta LTC, Rodrigues V, Violatti-Filho JR, Teixeira Neto BA, Tavares VM, Bernal ECBA, Souza DM, Araujo MS, de Lima Pereira SA, Rodrigues DBR. Modulation of Matrix Metalloproteinase 14, Tissue Inhibitor of Metalloproteinase 3, Tissue Inhibitor of Metalloproteinase 4, and Inducible Nitric Oxide Synthase in the Development of Periapical Lesions. *J Endod*. 2017 Jul;43(7):1122-1129. doi: 10.1016/j.joen.2017.02.020. Epub 2017 May 17. PMID: 28527839.
<https://doi.org/10.1016/j.joen.2017.02.020>
7. Chojnowska S., Baran T., Wilińska I., Sienicka P., Cabaj-Wiater I., Knaś M. Human Saliva as a Diagnostic Material. *Adv. Med. Sci*. 2018;63:185-191.
<https://doi.org/10.1016/j.advms.2017.11.002>
8. Dezerega A, Madrid S, Mundi V, Valenzuela MA, Garrido M, Paredes R, García-Sesnich J, Ortega AV, Gamonal J, Hernández M. Pro-oxidant status and matrix metalloproteinases in apical lesions and gingival crevicular fluid as potential biomarkers for asymptomatic apical periodontitis and endodontic treatment response. *J Inflamm (Lond)*. 2012 Mar 21;9(1):8. doi: 10.1186/1476-9255-9-8. PMID: 22436166; PMCID: PMC3358239.
<https://doi.org/10.1186/1476-9255-9-8>
9. Forman HJ, Bernardo A, Davies KJ. What is the concentration of hydrogen peroxide in blood and plasma? *Arch Biochem Biophys*. 2016 Aug 1;603:48-53. doi: 10.1016/j.abb.2016.05.005. Epub 2016 May 9. PMID: 27173735.
<https://doi.org/10.1016/j.abb.2016.05.005>
10. Francisconi CF, Colavite PM, Fonseca AC, Azevedo MCS, Tabanez AP, Melchiades JL, Vieira AE, Repeke CEP, Claudino M, Garlet GP.

- Microtomographic, histomorphometric, and molecular features show a normal alveolar bone healing process in iNOS-deficient mice along a compensatory upregulation of eNOS and nNOS isoforms. *J Appl Oral Sci.* 2023 Mar 20;31:e20220436. doi: 10.1590/1678-7757-2022-0436. eCollection 2023. <https://doi.org/10.1590/1678-7757-2022-0436>
11. Galler KM, Weber M, Korkmaz Y, Widbiller M, Feuerer M. Inflammatory Response Mechanisms of the Dentine-Pulp Complex and the Periapical Tissues. *Int J Mol Sci.* 2021 Feb 2;22(3):1480. doi: 10.3390/ijms22031480. PMID: 33540711; PMCID: PMC7867227. <https://doi.org/10.3390/ijms22031480>
 12. Georgiou AC, Cornejo Ulloa P, Van Kessel GMH, Crielaard W, Van der Waal SV. Reactive oxygen species can be traced locally and systemically in apical periodontitis: A systematic review. *Arch Oral Biol.* 2021 Sep;129:105167. doi: 10.1016/j.archoralbio.2021.105167. Epub 2021 May 27. PMID: 34126418. <https://doi.org/10.1016/j.archoralbio.2021.105167>
 13. Girotti AW. Lipid hydroperoxide generation, turnover, and effector action in biological systems. *J Lipid Res* 1998 Aug;39(8):1529-42. [https://doi.org/10.1016/S0022-2275\(20\)32182-9](https://doi.org/10.1016/S0022-2275(20)32182-9)
 14. Gomes C, Martinho FC, Barbosa DS, Antunes LS, Póvoa HCC, Baltus THL, Morelli NR, Vargas HO, Nunes SOV, Anderson G, Maes M. Increased Root Canal Endotoxin Levels are Associated with Chronic Apical Periodontitis, Increased Oxidative and Nitrosative Stress, Major Depression, Severity of Depression, and a Lowered Quality of Life. *Mol Neurobiol.* 2018 Apr;55(4):2814-2827. doi: 10.1007/s12035-017-0545-z. Epub 2017 Apr 28. PMID: 28455694. <https://doi.org/10.1007/s12035-017-0545-z>
 15. Grocholska P, Kowalska M, Bąchor R. Qualitative and Quantitative Mass Spectrometry in Salivary Metabolomics and Proteomics. *Metabolites.* 2023 Jan 20;13(2):155. doi: 10.3390/metabo13020155. <https://doi.org/10.3390/metabo13020155>
 16. Gulcin İ. Antioxidants and antioxidant methods: an updated overview. 2020 Mar;94(3):651-715. doi: 10.1007/s00204-020-02689-3. <https://doi.org/10.1007/s00204-020-02689-3>
 17. Hama S, Takeichi O, Hayashi M, Komiyama K, Ito K. Co-production of vascular endothelial cadherin and inducible nitric oxide synthase by endothelial cells in periapical granuloma. *Int Endod J.* 2006 Mar;39(3):179-84. doi: 10.1111/j.1365-2591.2006.01068.x. PMID: 16507070. <https://doi.org/10.1111/j.1365-2591.2006.01068.x>
 18. Hama S, Takeichi O, Saito I, Ito K. Involvement of inducible nitric oxide synthase and receptor for advanced glycation end products in periapical granulomas. *J Endod.* 2007 Feb;33(2):137-41. doi: 10.1016/j.joen.2006.11.011. PMID: 17258631. <https://doi.org/10.1016/j.joen.2006.11.011>
 19. Hernández-Ríos P, Pussinen PJ, Vernal R, Hernández M. Oxidative Stress in the Local and Systemic Events of Apical Periodontitis. *Front Physiol.* 2017 Nov 1;8:869. doi: 10.3389/fphys.2017.00869. PMID: 29163211; PMCID: PMC5672116. <https://doi.org/10.3389/fphys.2017.00869>
 20. Inchingolo F, Marrelli M, Annibali S, Cristalli MP, Dipalma G, Inchingolo AD, Palladino A, Inchingolo AM, Gargari M, Tatullo M. Influence of endodontic treatment on systemic oxidative stress. *Int J Med Sci.* 2013 Dec 6;11(1):1-6. doi: 10.7150/ijms.6663. PMID: 24396280; PMCID: PMC3880985. <https://doi.org/10.7150/ijms.6663>
 21. Jakovljevic A, Andric M, Nikolic N, Coric V, Krezovic S, Carkic J, Knezevic A, Beljic-

- Ivanovic K, Pljesa-Ercegovac M, Miletic M, Soldatovic I, Radosavljevic T, Jovanovic T, Simic T, Ivanovic V, Milasin J. Levels of oxidative stress biomarkers and bone resorption regulators in apical periodontitis lesions infected by Epstein-Barr virus. *Int Endod J*. 2018 Jun;51(6):593-604. doi: 10.1111/iej.12886. Epub 2018 Jan 30. PMID: 29315650.
<https://doi.org/10.1111/iej.12886>
22. Kabashima H, Nagata K, Maeda K, Iijima T. Interferon-gamma-producing cells and inducible nitric oxide synthase-producing cells in periapical granulomas. *J Oral Pathol Med*. 1998 Mar;27(3):95-100. doi: 10.1111/j.1600-0714.1998.tb01922.x. PMID: 9563799.
<https://doi.org/10.1111/j.1600-0714.1998.tb01922.x>
 23. Karabucak B, Setzer F. Criteria for the ideal treatment option for failed endodontics: surgical or nonsurgical? *Compend Contin Educ Dent*. 2007 Jun;28(6):304-10; quiz 311, 332. PMID: 17682612.
 24. Khurshid Z, Mali M, Naseem M, Najeeb S, Zafar MS. Human Gingival Crevicular Fluids (GCF) Proteomics: An Overview. *Dent J (Basel)*. 2017 Feb 22;5(1):12.
<https://doi.org/10.3390/dj5010012>
 25. Kudo H, Takeichi O, Makino K, Hatori K, Ogiso B. Expression of silent information regulator 2 homolog 1 (SIRT1) in periapical granulomas. *J Oral Sci*. 2018 Sep 23;60(3):411-417. doi: 10.2334/josnurd.17-0412. Epub 2018 Aug 12. PMID: 30101822.
<https://doi.org/10.2334/josnurd.17-0412>
 26. Loureiro C, Buzalaf MAR, Moraes FRN, Ventura TMO, Pelá VT, Pessan JP, Jacinto RC. Quantitative proteomic analysis in symptomatic and asymptomatic apical periodontitis. *International Endodontic Journal*, 54, 834-847, 2021. doi:10.1111/iej.13480
<https://doi.org/10.1111/iej.13480>
 27. Loureiro C, Buzalaf MAR, Pessan JP, Ventura TMO, Pelá VT, Ribeiro APF, Jacinto RC. Proteomic analysis of infected root canals with apical periodontitis in patients with type 2 diabetes mellitus: A cross-sectional study. *Int Endod J*. 2022 Sep;55(9):910-922. doi: 10.1111/iej.13794. Epub 2022 Jul 14. PMID: 35766999.
<https://doi.org/10.1111/iej.13794>
 28. Loureiro C, Buzalaf MAR, Ventura TMO, Pelá VT, Rodrigues GWL, Andrade JG, Pessan JP, Jacinto RC. Teeth with acute apical abscess vs. teeth with chronic apical periodontitis: a quantitative and qualitative proteomic analysis. *Clin Oral Investig*. 2023 Feb;27(2):591-601. doi: 10.1007/s00784-022-04754-w. Epub 2022 Nov 29. PMID: 36445466.
<https://doi.org/10.1007/s00784-022-04754-w>
 29. Majeed ZN, Philip K, Alabsi AM, Pushparajan S, Swaminathan D. Identification of Gingival Crevicular Fluid Sampling, Analytical Methods, and Oral Biomarkers for the Diagnosis and Monitoring of Periodontal Diseases: A Systematic Review. *Dis Markers*. 2016; 2016:1804727
<https://doi.org/10.1155/2016/1804727>
 30. Marton IJ, Balla G, Hegedus C, Redi P, Szilagyi Z, Karmazsin L, Kiss C. The role of reactive oxygen intermediates in the pathogenesis of chronic apical periodontitis. *Oral Microbiol Immunol*. 1993 Aug;8(4):254-7. doi: 10.1111/j.1399-302x.1993.tb00570.x. PMID: 8247615.
<https://doi.org/10.1111/j.1399-302x.1993.tb00570.x>
 31. Munteanu IG, Apetrei C. Analytical Methods Used in Determining Antioxidant Activity: A Review. *Int J Mol Sci*. 2021 Mar 25;22(7):3380. doi: 10.3390/ijms22073380.
<https://doi.org/10.3390/ijms22073380>
 32. Nair PN. Pathogenesis of apical periodontitis and the causes of endodontic failures. *Crit Rev Oral Biol Med*. 2004 Nov 1;15(6):348-81. doi:

- 10.1177/154411130401500604. PMID: 15574679.
<https://doi.org/10.1177/154411130401500604>
33. Nathan C, Cunningham-Bussell A. Beyond oxidative stress: an immunologist's guide to reactive oxygen species. *Nat Rev Immunol.* 2013 May;13(5):349-61. doi: 10.1038/nri3423. PMID: 23618831; PMCID: PMC4250048.
<https://doi.org/10.1038/nri3423>
 34. Nunez N, Erdogan O, Casey SM, Hernandez R, Tan S, Gibbs JL. Elevated Cytokine Levels in Gingival Crevicular Fluid of Teeth with Apical Periodontitis. *J Endod.* 2023 Mar 23:S0099-2399(23)00140-1. doi: 10.1016/j.joen.2023.03.010. Online ahead of print
<https://doi.org/10.1016/j.joen.2023.03.010>
 35. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016 Dec 5;5(1):210. doi: 10.1186/s13643-016-0384-4. PMID: 27919275; PMCID: PMC5139140.
<https://doi.org/10.1186/s13643-016-0384-4>
 36. Page M J, Moher D, Bossuyt P M, Boutron I, Hoffmann T C, Mulrow C D et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews *BMJ* 2021; 372 :n160 doi:10.1136/bmj.n160.
<https://doi.org/10.1136/bmj.n160>
 37. Peters, M.D.J.; Godfrey, C.M.; Khalil, H.; McInerney, P.; Parker, D.; Soares, C.B. Guidance for conducting systematic scoping reviews. *Int. J. Evid. Based Healthc.* 2015, 13, 141-146.
<https://doi.org/10.1097/XEB.0000000000000050>
 38. Pfafe T., Cooper-White J., Beyerlein P., Kostner K., Punyadeera C. Diagnostic Potential of Saliva: Current State and Future Applications. *Clin. Chem.* 2011;57:675-687.
<https://doi.org/10.1373/clinchem.2010.153767>
 39. Provenzano JC, Antunes HS, Alves FR, Rôças IN, Alves WS, Silva MR, Siqueira JF Jr. Host-Bacterial Interactions in Post-treatment Apical Periodontitis: A Metaproteome Analysis. *J Endod.* 2016 Jun;42(6):880-5. doi: 10.1016/j.joen.2016.02.013. Epub 2016 Apr 8. PMID: 27068493.
<https://doi.org/10.1016/j.joen.2016.02.013>
 40. Provenzano JC, Siqueira JF Jr, Rôças IN, Domingues RR, Paes Leme AF, Silva MR. Metaproteome analysis of endodontic infections in association with different clinical conditions. *PLoS One.* 2013 Oct 15;8(10):e76108. doi: 10.1371/journal.pone.0076108. eCollection 2013. PMID: 24143178
<https://doi.org/10.1371/journal.pone.0076108>
 41. Schmidt HH, Stocker R, Vollbracht C, Paulsen G, Riley D, Daiber A, Cuadrado A. Antioxidants in Translational Medicine. *Antioxid Redox Signal.* 2015 Nov 10;23(14):1130-43. doi: 10.1089/ars.2015.6393. Epub 2015 Aug 31. PMID: 26154592; PMCID: PMC4657516.
<https://doi.org/10.1089/ars.2015.6393>
 42. Shimauchi H, Takayama S, Narikawa-Kiji M, Shimabukuro Y, Okada H. Production of interleukin-8 and nitric oxide in human periapical lesions. *J Endod.* 2001 Dec;27(12):749-52. doi: 10.1097/00004770-200112000-00009. PMID: 11771582.
<https://doi.org/10.1097/00004770-200112000-00009>
 43. Sies H, Belousov VV, Chandel NS, Davies MJ, Jones DP, Mann GE, Murphy MP, Yamamoto M, Winterbourn C. Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. *Nat Rev Mol Cell Biol.* 2022 Jul;23(7):499-515. doi: 10.1038/s41580-022-00456-z. Epub 2022 Feb 21. PMID: 35190722.
<https://doi.org/10.1038/s41580-022-00456-z>
 44. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat Rev Mol Cell Biol.* 2020 Jul;21(7):363-383. doi:

- 10.1038/s41580-020-0230-3. Epub 2020 Mar 30. PMID: 32231263.Sies and Jones, 2022
<https://doi.org/10.1038/s41580-020-0230-3>
45. Silva M J B , Sousa L M A, Lara V P L, Cardoso F P, Júnior G M, Totola A H, Caliar M V, Romero O B, Silva G A B, Ribeiro-Sobrinho A P, Vieira L Q. The role of iNOS and PHOX in periapical bone resorption. J Dent Res 2011 Apr;90(4):495-500. doi: 10.1177/0022034510391792.
<https://doi.org/10.1177/0022034510391792>
 46. Şimşek OK, Baser U, Özgünler Ö, Demirci O, Aydın AF, Kucukgergin C, Yalcin F. Comparison of oxidative stress markers in the saliva, gingival crevicular fluid, and serum samples of pregnant women with gestational diabetes and healthy pregnant women. J Periodontal Res. 2023 May 8. doi: 10.1111/jre.13132. Online ahead of print.
<https://doi.org/10.1111/jre.13132>
 47. Subbarao KC, Nattuthurai GS, Sundararajan SK, Sujith I, Joseph J, Syedshah YP. Gingival Crevicular Fluid: An Overview. J Pharm Bioallied Sci. 2019 May;11(Suppl 2):S135-S139.
https://doi.org/10.4103/JPBS.JPBS_56_19
 48. Takeichi O, Saito I, Okamoto Y, Tsurumachi T, Saito T. Cytokine regulation on the synthesis of nitric oxide in vivo by chronically infected human polymorphonuclear leucocytes. Immunology. 1998 Feb;93(2):275-80. doi: 10.1046/j.1365-2567.1998.00413.x. PMID: 9616379; PMCID: PMC1364189.
<https://doi.org/10.1046/j.1365-2567.1998.00413.x>
 49. Taylor JJ, Preshaw PM. Gingival crevicular fluid and saliva. Periodontol 2000. 2016 Feb;70(1):7-10.
<https://doi.org/10.1111/prd.12118>
 50. Tibúrcio-Machado CS, Michelon C, Zanatta FB, Gomes MS, Marin JA, Bier CA. The global prevalence of apical periodontitis: a systematic review and meta-analysis. Int Endod J. 2021 May;54(5):712-735. doi: 10.1111/iej.13467. Epub 2021 Jan 22. PMID: 33378579.
<https://doi.org/10.1111/iej.13467>
 51. Tricco AC, Lillie E, Zarin W, O'Brien K, Colquhoun H, Kastner M, Levac D, Ng C, Sharpe JP, Wilson K, Kenny M, Warren R, Wilson C, Stelfox HT, Straus SE. A scoping review on the conduct and reporting of scoping reviews. BMC Med Res Methodol. 2016 Feb 9;16:15. doi: 10.1186/s12874-016-0116-4. PMID: 26857112; PMCID: PMC4746911.
<https://doi.org/10.1186/s12874-016-0116-4>
 52. Vengerfeldt V, Mändar R, Saag M, Piir A, Kullisaar T. Oxidative stress in patients with endodontic pathologies. J Pain Res. 2017 Aug 24;10:2031-2040. doi: 10.2147/JPR.S141366. PMID: 28894386; PMCID: PMC5584906.
<https://doi.org/10.2147/JPR.S141366>
 53. Żukowski P, Maciejczyk M, Waszkiel D. Sources of free radicals and oxidative stress in the oral cavity. Arch Oral Biol. 2018 Aug;92:8-17
<https://doi.org/10.1016/j.archoralbio.2018.04.018>
 54. Ye, L., Cao, L., Song, W., Yang, C., Tang, Q., Yuan, Z."Interaction between apical periodontitis and systemic disease (Review)". International Journal of Molecular Medicine 52, no. 1 (2023): 60. <https://doi.org/10.3892/ijmm.2023.5263>
<https://doi.org/10.3892/ijmm.2023.5263>

TABLES

Table 1. Eletronic database and search strategy

Database	Search Strategy (January, 2023)	Results
PubMed (http://www.ncbi.nlm.nih.gov/pubmed)	((“Apical Alveolar Abscess” OR “Apical Periodontitis” OR “Dental Pulp Cavity” OR “Dental Pulp Disease” OR “Dental Pulp Necrosis” OR “Endodontic Inflammation” OR “Endodontics” OR “Periapical Abscess” OR “Periapical Disease” OR “Periapical Periodontitides” OR “Periapical Periodontitis” OR “Pulp Canal” OR “Pulpitides” OR “Pulpitis” OR “Root Canal” OR “Teeth” OR “Tooth”) AND (“Nitro Oxidative Stress” OR “Nitro-Oxidative Stress” OR “Nitrogen Oxides” OR “Nitrosative Stress” OR “Oxidative and Nitrosative Stress” OR “Oxidative Cleavage” OR “Oxidative Damage” OR “Oxidative DNA Damage” OR “Oxidative Injury” OR “Oxidative Nitrative Stress” OR “Oxidative Stress” OR “Oxidative Stress Injury” OR “Reactive Nitrogen Species” OR “Redox Balance”))	546
LILACS (http://lilacs.bvsalud.org/)	((“oxidative stress”) AND (“teeth” OR “tooth” OR “apical periodontitis” OR “Root Canal”)) AND (db:(“LILACS”))	41
SciELO (http://www.scielo.org/)	(Oxidative Stress OR Nitro Oxidative Stress OR Nitro-Oxidative Stress) AND (Necrosis OR Endodontics OR Tooth OR Teeth OR Apical Periodontitis OR Endodontic Inflammation)	311
Embase (http://www.embase.com)	('apical alveolar abscess' OR 'apical periodontitis'/exp OR 'apical periodontitis' OR 'dental pulp cavity'/exp OR 'dental pulp cavity' OR 'dental pulp disease'/exp OR 'dental pulp disease' OR 'dental pulp necrosis'/exp OR 'dental pulp necrosis' OR 'endodontic inflammation'/exp OR 'endodontic inflammation' OR 'endodontics'/exp OR 'endodontics' OR 'periapical abscess'/exp OR 'periapical abscess' OR 'periapical disease'/exp OR 'periapical disease' OR 'periapical periodontitides' OR 'periapical periodontitis'/exp OR 'periapical periodontitis' OR 'pulp canal' OR 'pulpitides' OR 'pulpitis'/exp OR 'pulpitis' OR 'root canal'/exp OR 'root canal' OR 'teeth'/exp OR 'teeth' OR 'tooth'/exp OR 'tooth') AND ('nitro oxidative stress' OR 'nitro-oxidative stress' OR 'nitrogen oxides'/exp OR 'nitrogen oxides' OR 'nitrosative stress'/exp OR 'nitrosative stress' OR 'oxidative and nitrosative stress' OR 'oxidative cleavage'/exp OR 'oxidative cleavage' OR 'oxidative damage'/exp OR 'oxidative damage' OR 'oxidative dna damage'/exp OR 'oxidative dna damage' OR 'oxidative injury'/exp OR 'oxidative injury' OR 'oxidative nitrative stress' OR 'oxidative stress'/exp OR 'oxidative stress' OR 'oxidative stress injury' OR 'reactive nitrogen species'/exp OR 'reactive nitrogen species' OR 'redox balance')	1.206
Scopus (http://www.scopus.com/)	TITLE-ABS-KEY ((("Apical Alveolar Abscess" OR "Apical Periodontitis" OR "Dental Pulp Cavity" OR "Dental Pulp Disease" OR "Dental Pulp Necrosis" OR "Endodontic Inflammation" OR "Endodontics" OR "Periapical Abscess" OR "Periapical Disease" OR "Periapical Periodontitides" OR "Periapical Periodontitis" OR "Pulp Canal" OR "Pulpitides" OR "Pulpitis" OR "Root Canal" OR "Teeth" OR "Tooth") AND ("Nitro Oxidative Stress" OR "Nitro-Oxidative Stress" OR "Nitrogen Oxides" OR "Nitrosative Stress" OR "Oxidative and Nitrosative Stress" OR "Oxidative Cleavage" OR "Oxidative Damage" OR "Oxidative DNA Damage" OR "Oxidative Injury" OR "Oxidative Nitrative Stress" OR "Oxidative Stress" OR "Oxidative Stress Injury" OR "Reactive Nitrogen Species" OR "Redox Balance")))	993
Web of Science (http://apps.webofknowledge.com/)	((“Apical Alveolar Abscess” OR “Apical Periodontitis” OR “Dental Pulp Cavity” OR “Dental Pulp Disease” OR “Dental Pulp Necrosis” OR “Endodontic Inflammation” OR “Endodontics” OR “Periapical Abscess” OR “Periapical Disease” OR “Periapical Periodontitides” OR “Periapical Periodontitis” OR “Pulp Canal” OR “pulpitis” OR “Pulpitis” OR “Root Canal” OR “Teeth” OR “Tooth”) AND (“Nitro Oxidative Stress” OR “Nitro-Oxidative Stress” OR “Nitrogen Oxides” OR “Nitrosative	776

	Stress" OR "Oxidative and Nitrosative Stress" OR "Oxidative Cleavage" OR "Oxidative Damage" OR "Oxidative DNA Damage" OR "Oxidative Injury" OR "Oxidative Nitrative Stress" OR "Oxidative Stress" OR "Oxidative Stress Injury" OR "Reactive Nitrogen Species" OR "Redox Balance"))	
OATD (https://oatd.org/)	((("Apical Alveolar Abscess" OR "Apical Periodontitis" OR "Dental Pulp Cavity" OR "Dental Pulp Disease" OR "Dental Pulp Necrosis" OR "Endodontic Inflammation" OR "Endodontics" OR "Periapical Abscess" OR "Periapical Disease" OR "Periapical Periodontitides" OR "Periapical Periodontitis" OR "Pulp Canal" OR "Pulpitides" OR "Pulpitis" OR "Root Canal" OR "Teeth" OR "Tooth") AND ("Nitro Oxidative Stress" OR "Nitro-Oxidative Stress" OR "Nitrogen Oxides" OR "Nitrosative Stress" OR "Oxidative and Nitrosative Stress" OR "Oxidative Cleavage" OR "Oxidative Damage" OR "Oxidative DNA Damage" OR "Oxidative Injury" OR "Oxidative Nitrative Stress" OR "Oxidative Stress" OR "Oxidative Stress Injury" OR "Reactive Nitrogen Species" OR "Redox Balance"))	90
DANS Easy (https://easy.dans.knaw.nl)	((("Oxidative Stress") AND ("Teeth" OR "Tooth" OR "Apical Periodontitis" OR "Root Canal"))	9
Total		3.972

OATD = Open Access Theses and Dissertations; DANS = Data Archiving and Networked Services.

Table 2. Summary of the main characteristics of the included studies.

Author, Year	Country	Population* (F/M; Age, y)	Study design	Inclusion Criteria	Exclusion Criteria	Systemic health condition**
Marton <i>et al.</i> , 1993	USA	22 (14/8; 25-29)	OS	RAL (3-5 mm) Teeth endodontically treated	NR	Healthy
Kabashima <i>et al.</i> , 1998	Japan	10 (5/5; 17-64)	OS	NR	Antibiotic, NSAIDs or analgesic treatment (3-months prior study); Systemic disease	Healthy
Takeichi <i>et al.</i> , 1998	Japan	30 (13/17; 28-56)	OS	RAL (15-25mm)	Systemic disease; Antibiotic treatment (6-months prior study)	Healthy
Takeichi <i>et al.</i> , 1999	Japan	29 (12/17; 26-62)	OS	RAL (15-25mm)	Systemic disease; Antibiotic treatment (6-months prior study)	Healthy
Shimauchi <i>et al.</i> , 2001	Japan	27 teeth (ND)	OS	Clinical and/or radiographic diagnostic of pulp necrosis	Systemic disease; Lesions related to marginal periodontitis	Healthy
Hama <i>et al.</i> , 2006	Japan	31 (15/16; 19-79)	OS	RAL	Systemic diseases; Antibiotic treatment (6-months prior study)	Healthy (AL)
Hama <i>et al.</i> , 2007	Japan	37 (19/18; 19-79)	OS	RAL	Systemic diseases; Antibiotic treatment (6-months prior study)	Healthy
Dezerega <i>et al.</i> , 2012	Chile	23 (NR)	OS	RAL (> 3mm diameter)	Periodontal attachment loss ($\leq$ 2 mm); Increased probing depths ($\leq$ 3 mm); Current smokers; Antibiotic or NSAIDs treatment (6-months prior study)	Healthy

					Any potential treatment or condition that could alter the results;	
Inchingolo <i>et al.</i> , 2014	Italy	136 (57/79; 30-68)	OS	RAL (2 cm or less that did not affect anatomical structures)	Antibiotic, NSAIDs or analgesic treatment (3-months prior study); Smokers; Obesity; Systemic diseases; < 25 teeth; Poor oral hygiene; Evolution with no healing of chronic periodontitis	Healthy
Cotti <i>et al.</i> , 2015	Italy	81 (41/40; ≈ 31)	OS	20-40 years old; RAL; Healthy	Periodontal disease; Non endodontic lesions; Chronic inflammatory disease; Cardiovascular risk factors; Use of contraceptives (female)	Healthy
Gomes <i>et al.</i> , 2017	Brazil	47 (NR)	OS	≥ 18 years old; Able to read, write Portuguese language and planned to have their teeth extracted.	Current or lifetime axis-I diagnoses; Substances abuse; Major medical disorder	Depression
Vengerfeldt <i>et al.</i> , 2017	Estonia	55 (28/27; 18-76)	OS	Single AL lesion; RAL (2 cm or less that did not affect anatomical structures)	Antibiotic, NSAIDs or analgesic treatment (3-months prior study); Current smokers; Obesity; Pregnancy; Systemic inflammatory or metabolic diseases condition; Poor oral hygiene	Healthy
Jakovljevic <i>et al.</i> , 2018	Servia	60 (33/27; NR)	OS	Good general health, with no severe systemic disease who required surgical apicoectomy due to the failure of root canal treatment.	Patients with periodontally involved teeth (probing depth > 4 mm, with periodontal bone loss), vertical root fracture, immature	EBV positive

					teeth with open apices, immunocompromised, or patients treated with antibiotics, antiviral or immunosuppressive therapy 3 months before the examination.	
Kudo <i>et al.</i> , 2018	Japan	17 (11/6; 20-74)	CC	Persistent periapical periodontitis, referred by general practitioners to Department of Endodontics	NR	Healthy
Bains <i>et al.</i> , 2021	India	11 (NR; 21.09 ± 3.24)	COORTE	Periapical condition according to periapical index by Ostravik (at least 1 tooth).	Antibiotic, NSAIDs or analgesic treatment (3-months prior study); Systemic diseases; Less than 25 teeth; Poor oral hygiene	Healthy
Loureiro <i>et al.</i> , 2021	Brazil	18 (NR)	OS	Asymptomatic and symptomatic tooth with necrotic pulp and RAL regardless of its size.	Antibiotic treatment (3-months prior study); Systemic diseases; Teeth that could not be isolated; Teeth with exposed root canals; Edema in periapical tissues; Advanced periodontal disease; Incomplete root formation; Dental trauma history; False-negative response to the cold sensitivity test	Healthy
Loureiro <i>et al.</i> , 2022	Brazil	18 (NR; 18-60)	OS	Patients with a metabolic control status of HbA1c ≥ 7.5% were included in the diabetic group. Primary endodontic infections with RAL 2.5mm ≥ in diameter.	Systemic: Current smokers; Hypertension; Autoimmune diseases; Pregnancy; Chronic liver disease; Chronic kidney disease; Transplant; Antibiotic treatment (3-months prior study);	Diabetes mellitus

Loureiro <i>et al.</i> , 2023	Brazil	9 (NR; 18-60)	OS	Teeth with necrotic pulp (negative response to the cold sensitivity test); RAL $\geq$ 2.5 mm in diameter; Completely asymptomatic or w/ a slight sensitivity to percussion or palpation.	Teeth: spontaneous pain and/or pain when bitten/eating, tenderness to percussion, teeth that could not be isolated, exposed root canal, dental trauma, edema in periapical tissues, advanced periodontal disease or incomplete root formation. Any treatment (3-months prior study); Systemic disease; Pockets $\geq$ 4 mm and/or bleeding upon stimulus; Incomplete root formation; Root canals exposed to the oral cavity; Fistula; Teeth that could not be isolated	Healthy
----------------------------------	--------	------------------	----	--	--	---------

** For all studies that presented systemic diseases, a healthy control group was observed; *Total number of patients considering only the groups used in this scoping review; $\approx$ approximately; AAA: acute apical abscess; AL: apical lesion; ANL: Analytic longitudinal; AP: apical periodontitis; CT: control; EBV: Epstein–Barr virus; iNOS: nitric oxide synthase; NR: Not related by the author; NSAIDs: non-steroidal anti-inflammatory drugs; CC: Case-Control; OS: Observational study; RAL: radiolucent apical lesion.

Table 3. Summary of specific results of included studies

Author, Year	Sample acquire (n)	Intervention	OS-types analyzed	Evaluation method	OS outcome
Marton <i>et al.</i> , 1993	GT (8) AL (22)	Tooth extraction Periapical surgery	(1) MDA [-] (2) SOD [-] (3) GSH-Px [+]	(1), (2) and (3) Biochemistry analysis	(1) AL > CT (2) AL > CT (3) AL < CT
Kabashima <i>et al.</i> , 1998	PDL (2) AL (8)	Tooth extraction Periapical surgery	(1) iNOS [-]	(1) Immunohistochemistry	(1) AL+ and CT-
Takeichi <i>et al.</i> , 1998	AL (10) Periapical exudates (20)	Periapical surgery	(1) iNOS [-] (2) NO ₂ [-]	(1) Immunohistochemistry and Immunofluorescence (2) Biochemistry analysis	(1) + (2) +
Takeichi <i>et al.</i> , 1999	AL (20)	Periapical surgery	(1) iNOS [-]	(1) Immunohistochemistry and Immunofluorescence	(1) +
Shimauchi <i>et al.</i> , 2001	Paper points over the apex	Endodontic treatment	(1) NO ₂ [-]	(1) Biochemistry analysis	(1) +
Hama <i>et al.</i> , 2006	AL	Periapical surgery	(1) iNOS [-]	(1) Immunohistochemistry and Immunofluorescence	(1) +
Hama <i>et al.</i> , 2007	AL	Periapical surgery	(1) iNOS [-]	(1) Immunohistochemistry	(1) +
Dezerega <i>et al.</i> , 2012	AL (10) PDL (13) GCF (16)	Tooth extraction(AL, PDL) endodontic treatment (GCF) contralateral tooth (GCF)	(1) TOS [-] (2) TAS [+]	(1) Biochemistry analysis (2) Biochemistry analysis	(1) AL > PDL (2) AL = PDL
Inchingolo <i>et al.</i> , 2014	Plasma - Blood sample	Endodontic treatment	(1) TOS [-] (2) TAS [+]	(1) Biochemistry analysis (2) Biochemistry analysis	(1) AL > CT (2) AL < CT
Cotti <i>et al.</i> , 2015	Serum - Blood sample	None	(1) ROS [-]	(1) Biochemistry analysis	AL > CT ♀ AL = CT ♂

Gomes <i>et al.</i> , 2017	Plasma - Blood sample	None	(1) AOPP [-] (2) NO ₂ [-] (3) LOOH [-] (4) TRAP [+] (5) PON1 [+]	(1) Biochemistry analysis	(1) AL > CT (2) AL > CT (3) AL > CT (4) AL > CT (5) AL > CT
Vengerfeldt <i>et al.</i> , 2017	Saliva samples Pulp samples Previous root filling	Endodontic treatment	(1) TPX (OSI) [-] (2) TAC (OSI) [+] (3) MPO [+] (4) 8-EPI [+]	(1) Biochemistry analysis (2) Biochemistry analysis (3) ELISA (4) ELISA	(1) Saliva = Pulp (AL > CT) (2) Saliva = Pulp (AL > CT) (3) Saliva > Pulp (AL > CT) (4) Saliva = Pulp (AL > CT)
Jakovljevic <i>et al.</i> , 2018	Pulp tissues (20) AL (60)	Extraction (CT) Periapical surgery (AL)	(1) 8-OHdG [-] (2) GSH/ GSSG [+]	(1) ELISA (2) ELISA	(1) AL > CT (2) AL > CT
Kudo <i>et al.</i> , 2018	PDL (control, 10) AL (7)	Extraction (CT) Periapical surgery (AL)	(1) SIRT 1 [+] (2) 8-OHdG [-]	(1) Immunofluorescence (2) Immunofluorescence	(1) AL+ and CT- (2) AL+ and CT-
Bains <i>et al.</i> , 2021	Venous blood samples	Endodontic treatment	(1) GSH [+]	(1) Biochemistry analysis	(1) = GSH T ₀ (2) = GSH T ₁
Loureiro <i>et al.</i> , 2021	Paper points over the apex	NR	(1) Proteomic analysis	(1) liquid chromatography coupled to mass spectrometry	OS-related proteins expressed (Peroxiredoxin-1, Peroxiresodixin-2, Peroxiredoxin 2_isoform CRA_a, Myeloperoxidase)
Loureiro <i>et al.</i> , 2022	Paper points over the apex	NR	(1) Proteomic analysis	(1) liquid chromatography coupled to mass spectrometry	OS-related proteins expressed (Peroxiredoxin-1, Peroxiresodixin-2, Peroxiredoxin 2_isoform CRA_a, Eosinophil peroxidase, Myeloperoxidase, Glyceraldehyde-3-phosphate dehydrogenase)

Loureiro <i>et al.</i> , 2023	Paper points over the apex	NR	(1) Proteomic analysis	(1) liquid chromatography coupled to mass spectrometry	OS-related proteins expressed (Eosinophil peroxidase, Glyceraldehyde-3-phosphate dehydrogenase, Glutathione S-transferase P, Myeloperoxidase, Peroxiredoxin-5_mitochondrial)
-------------------------------	----------------------------	----	------------------------	--	--

*Total number of patients considering only the groups used in this scoping review

[-] oxidant; [+] antioxidant; - negative for cells; + positive for cells; < significantly less oxidative stress; = not statistically significant difference; > significantly greater oxidative stress; ♀ female population; ♂ male population; 8-EPI: 8-isoprostanes; 8-OHdG = 8-hydroxy-2'-deoxyguanosine; AGP: Alpha-1 acid glycoprotein; AL: apical lesion; AOPP: advanced oxidation protein products; CT: control; GCF: gingival crevicular fluid; GSH-Px: glutathione peroxidase; GSH: glutathione; GSSG: glutathione disulfide; GT: gingival tissue, H₂O₂: hydrogen-peroxide; iNOS: inducible nitric oxide synthase; LOOH: lipid peroxides; MDA: malondialdehyde; MPO: Myeloperoxidase; NO₂⁻: nitrite; NOx: nitric oxide metabolites; NR: Not related by the author; O₂⁻: superoxide anion; OS: oxidative stress; OSI: Oxidative stress index; PDL: periodontal ligament; PON1: paraoxonase; ROS: reactive oxygen species; SIRT1 = sirtuin 1; SOD: Superoxide Dismutase; T₀: before intervention; T₁: after 30-days completion of endodontic therapy; TAC: total antioxidant capacity; TAS: total antioxidant status; TOS: total oxidant status; TPX: total peroxide concentrations; TRAP: total radical trapping antioxidant parameter; VitC= Vitamin C.

FIGURES

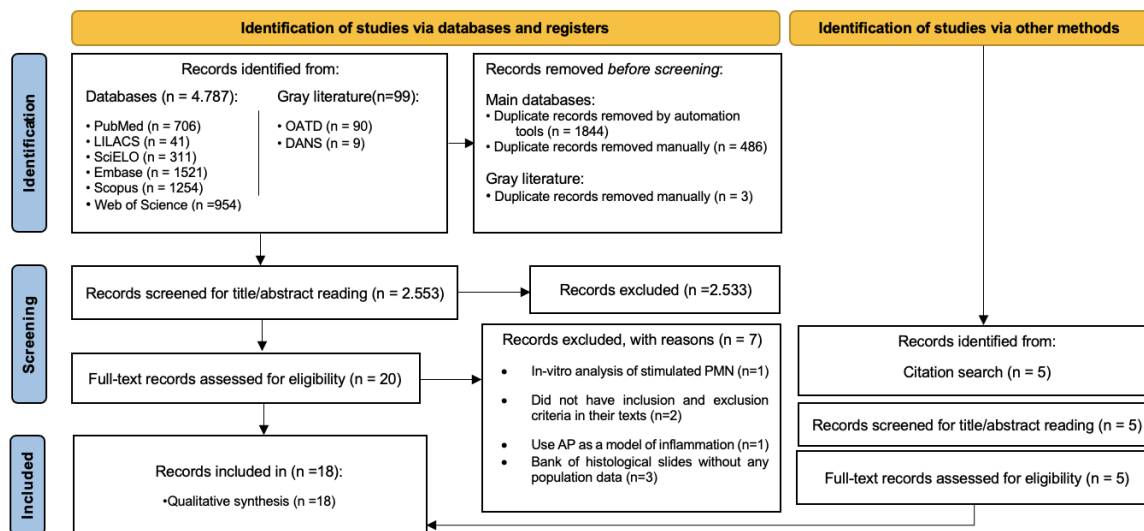


Figure 1. PRISMA flow diagram

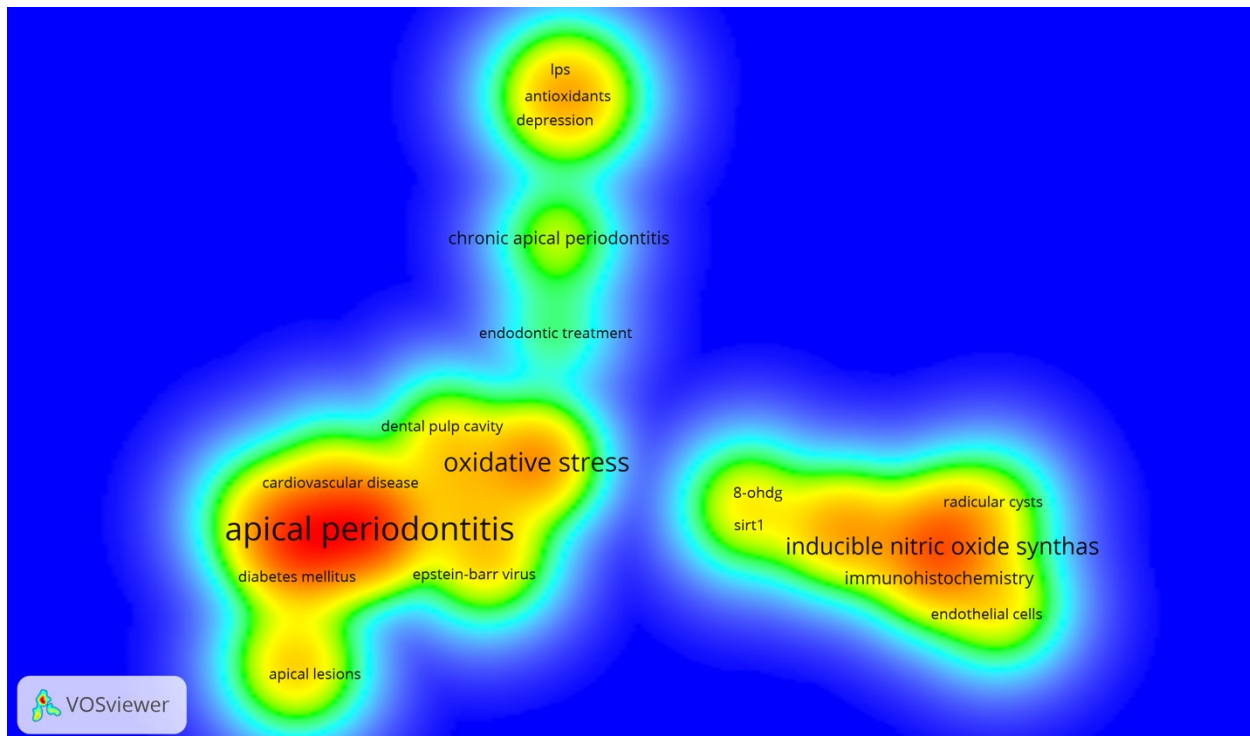


Figure 2. Hot topics among 213 keywords were identified using density visualization. Red–yellow–green–blue color density was used; red represents the highest and blue the lowest density of keywords co-occurrence.

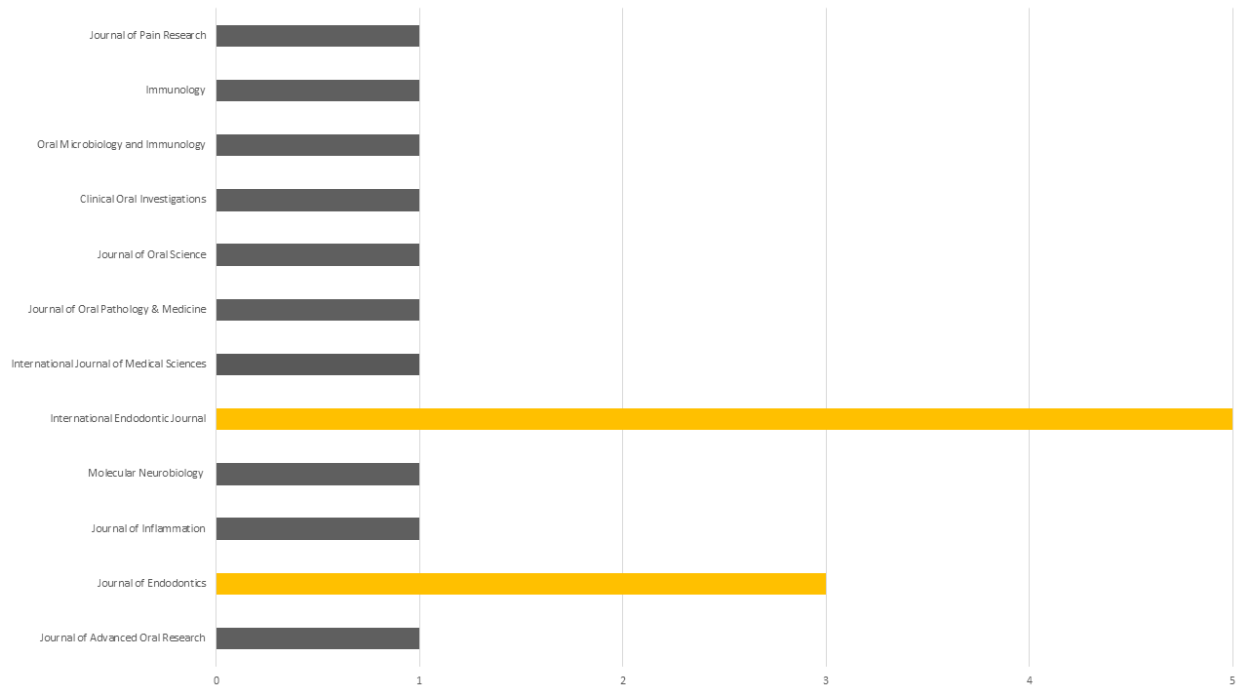


Figure Supplementary 1. Journals that published at least one article on apical periodontitis and oxidative stress.

**Endodontic infection as a
probable origin of post
streptococcal glomerulonephritis -
a case report**

Macedo Signorelli NS, Machado JR, dos Reis, MAR, Moura CCG

Type of article: Original

Title of the article: Impact of endodontic treatment in acute systemic diseases: a case report

Keywords: Renal Acute Disease, Endodontic Medicine, Apical Periodontitis

Author information:

1. Nara Sarmiento Macedo Signorelli - MS Student
2. Juliana Reis Machado - Professor, PhD
3. Marlene A dos Reis - Professor, PhD
4. Camilla Christian Gomes Moura - Professor, PhD

Department(s), institution(s), and email address

Post-graduation Program in Dentistry, School of Dentistry, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil. profnarasignorelli@gmail.com
<https://orcid.org/0000-0002-8460-7795>

Department of General Pathology, School of Medicine, Federal University of Triângulo Mineiro, Uberaba, Minas Gerais, Brazil. juliana.patologiageral@gmail.com
<https://orcid.org/0000-0002-8673-7788>

Department of General Pathology, School of Medicine, Federal University of Triângulo Mineiro, Uberaba, Minas Gerais, Brazil. mareispatologia@gmail.com
<https://orcid.org/0000-0003-2523-2097>

Department of Endodontics and Dental Materials, School of Dentistry, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil. camillamoura@ufu.br
<https://orcid.org/0000-0002-5653-8403>

Institution to which the work should be attributed

Department of Endodontic and Dental Materials, School of Dentistry, Federal University of Uberlândia, Campus Umuarama, Av. Pará, 1720, Bloco 2G. camillamoura@ufu.br

Corresponding author

Prof. Dr. Juliana Reis Machado

Department of Biological Sciences, School of Medicine, Federal University of Triângulo Mineiro, Praça Manoel Terra - até 186/187 - Estados Unidos ZIP code 38015050 - Uberaba, MG – Brazil juliana.patologiageral@gmail.com

Sources of support

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES) - Finance Code 001. We are also thankful for the support of Conselho Nacional de Desenvolvimento Científico e Tecnológico - Brazil (CNPq) and Fundação de Amparo à Pesquisa do Estado de Minas Gerais – Brazil (FAPEMIG).

Disclosure statement

The authors deny any conflicts of interest related to this study.

Clinical relevance statement

Post-streptococcal glomerulonephritis (PSGN) is an acute kidney disease, caused by streptococcus, and has been related to skin and respiratory tract infections, however, endodontic infections should be raised as an etiological factor when the usual factors are not identified.

ABSTRACT

Post-streptococcal glomerulonephritis (PSGN) is usually triggered by skin and upper respiratory tract infections, leading to renal injury. This case report presents a confirmed case of PSGN through laboratory tests and renal biopsy, in which the probable causal factor was an endodontic infection in a tooth with pulp necrosis. After endodontic treatment, the patient did not experience a recurrence of the disease, demonstrating the importance of careful dental examination in cases of PSGN with no detected causal factor, in order to proceed with appropriate treatment.

Keywords: Renal Acute Disease, Endodontic Medicine, Apical Periodontitis

INTRODUCTION

Glomerulonephritis (GN) constitutes one of the main causes of renal injury and often requires biopsy for etiological diagnosis (Pesce et al., 2021). Among GN triggered by immune-mediated inflammatory response, those associated with infection are commonly found in underdeveloped countries (Rodriguez-Iturbe & Haas, 2016A; Satoskar et al., 2020). Although they can be triggered by bacterial, viral, parasitic, or fungal infections, "infection-associated GN" is typically associated with β -hemolytic group A streptococcus infections originating from the skin or respiratory tract, and occasionally by streptococci from groups C or G (Rodriguez-Iturbe & Haas, 2016B; Satoskar et al., 2020). These can develop after complete resolution of the infection and a latent period, as well as being associated with an ongoing infection (Satoskar et al., 2020).

Children are the main population affected by post-streptococcal glomerulonephritis (PSGN), although it can also affect debilitated elderly individuals and, to a lesser extent, young adults (Rodriguez-Iturbe & Haas, 2016B; Pesce et al., 2021; Dhakal et al., 2023). While the development of end-stage renal disease (ESRD) due to PSGN is rare, the overall prognosis is generally worse in adults than in children (Pinto et al., 2001; Pesce et al., 2021), especially if other risk factors such as diabetes mellitus coexist (Rodriguez-Iturbe & Haas, 2016B).

Streptococcus has been identified as one of caries microbiome species related to dental caries development (Zhu et al. 2023), and to a lesser extent related to the development of endodontic infections (Georgiou et al. 2023).

Although, to our knowledge, there are no data in the literature to date regarding PSGN triggered by endodontic infection, this case report points to this probable association. This case report describes a case of PSGN confirmed through clinical, laboratory, and biopsy examinations, in which the probable etiology indicated by the physician could be an oral infection. The patient was

referred to the dentistry service, where a single tooth with extensive caries and pulp necrosis was detected. Considering that the treatment of PSGN, in general, is aimed at eliminating the underlying infection and controlling the symptoms, this case report highlights the importance of a endodontic evaluation in cases of PSGN, in order to proceed with the appropriate treatment for disease remission.

CASE REPORT

A 36-year-old male, asymptomatic, was referred to our clinic for dental evaluation November 12th, 2020 after previous acute renal injury.

Medical History

The patient was in good health until October 7th, 2020 when was admitted to the healthcare unit due to generalized edema, arterial hypertension, and pleural effusion. He was seen by several physicians and submitted to evaluation of renal function. All the tests performed on the date of admission and during the time the patient remained hospitalized and subsequently after discharge are presented in Table 1. His history was suggestive of glomerulonephritis.

In October 28th, 2020 the patient was submitted to kidney biopsy which confirmed PSGN (Fig 1) Without apparent cause, no reported recent infection of the airways, ears, or skin. During the medical history, the patient denied having a diagnosis of COVID-19. The patient remained hospitalized for 20 days, and his discharge medications included Losartan Potassium 50 mg, Furosemide 40 mg, Amlodipine Besylate 5 mg, Prednisone 60 mg, and Hydralazine Hydrochloride 100 mg daily.

Dental History

The patient was asymptomatic at initial examination and stated that he had ever pain six months before in the upper left first molar area after restorative treatment failed, which disappear in few days.

Oral Examination and Diagnostics Tests

A careful clinical evaluation and a complete periapical radiographic series was performed looking for possible infectious foci (Fig. 2). The soft tissues of the mouth and pharynx were normal. Tooth 46 was missing, which reported extraction approximately 20 years ago, impacted third molars, no exposure to the oral environment and no apparent caries (Fig.2). During the periodontal evaluation, did not show pockets and/or probing depths greater than 2 mm, no bleeding points, tooth mobility or gingivitis. Some bacterial plaque foci could be observed, but without repercussions on the periodontal clinical condition. Only 26 (Fig. 3) had an extensive carious lesion and apparent exposure of the pulp chamber to the oral environment. The referred teeth did not respond to electrical or thermal testing which in conjunction with the radiographic findings was indicative of pulpal necrosis, being indicated to endodontic treatment. The probable etiology was extensive caries improperly restored with composite resin, which fell and exposed the tooth to microbial contamination and consequent necrosis.

Consultation with the Physician

The physician who performed the clinical treatment of PSGN was contacted and advised of the endodontic treatment plan which consisted of root canal therapy for teeth 26 and subsequent restorative treatment. Since there was no evidence of pain, swelling, or temperature elevation, short-term antibiotic coverage with two grams of amoxicillin 1 hour before the first appointment was agreed upon.

Endodontic Therapy

The patient was placed on prophylactic antibiotic coverage as outlined above, underwent prophylaxis and supragingival scaling in all quadrants and then the endodontic treatment started in 11/12/2020. All endodontic therapy was performed under local anesthesia, 2% lidocaine with 1:100,000 epinephrine. Routine endodontic access openings were made on the teeth under a rubber dam and all four root canals orifice were located with the help of loupe (Zeiss Pico; Zeiss, Gottingen, Germany) at 3.5x magnification. The working lengths were determined by an apex locator (Romiapex A-15, Romidan Dental Solution, Kiryat-Ono, Israel) and confirmed radiographically. The canals were enlarged with Proglider® #16.02 (Dentsply, Ballaigues, Switzerland), and the preparation was completed with Wave One Gold® #25.07 (Dentsply). Apical preparations were enlarged to a #40 K-file (Dentsply). The canals were irrigated with approximately 80 mL of 2% Nicoll, and final irrigation activated with EasyClean device (Easy Equipamentos Odontológicos, São Paulo, Brazil). Subsequently, calcium hydroxide (Ultracal XS; Ultradent Products Inc, South Jordan, UT) was placed as a temporary dressing for 15 days. The access cavity was temporarily sealed with glass ionomer (Ketac Nano, 3 M ESPE, St Paul, MN). The canals were obturated at a second appointment at 11/27/2020, using AHPlus (Dentsply) (Fig.10), Tagger's hybrid technique and vertical condensed gutta-percha using cold pressers. The cavity was restored during the same visit with composite (Filtek Z350 XT, 3M ESPE), and dental occlusion was checked. The patient was invited to return for endodontic evaluation at 1, 3, 6, 9, 12, 18, and 24 months after treatment completion. The patient returned for follow-up at 1, 18, and 24 months (July 2022) and was completely symptom-free. Clinical examination revealed that the tooth showed no sensitivity to percussion or palpation, no mobility, and probing depths were within the normal range. Radiographic and tomographic assessments showed a continuous

periodontal ligament space with no signs of apical periodontitis. (Fig. 4).

Medical status

During this period, the patient continued to be monitored by a nephrologist, showing complete regression of the glomerulonephritis condition. Blood pressure was controlled as of January 2021, allowing for the discontinuation of antihypertensive medications in March 2021. Normalization of PCR, Urea, and Creatinine levels was observed in the laboratory tests conducted in 2021 (Table 1). New laboratory tests were requested from the patient during their annual follow-up in 2022, and the monitoring showed even lower levels of the mentioned markers (Table 1).

DISCUSSION

The literature presents several publications that associate poor oral health with increased risks of complications in chronic kidney disease patients (Schmalz et al., 2020; Kreher et al., 2023), as well as a lower risk of mortality among dialysis patients who received adequate endodontic treatment (Chiu et al., 2021). However, the impact of periodontal disease on the development of renal alterations is not well understood (Segura-Egea et al., 2015; Cintra et al., 2021). In this case report, we present a case of post-streptococcal glomerulonephritis (PSGN) in which the main causal relationship identified was an endodontic infection.

For a physician to suspect PSGN, the patient should have a history of untreated streptococcal infection occurring one to six weeks before the development of the characteristic clinical manifestations of the disease. Infections commonly associated with PSGN originate from the skin, throat, and ears, and the initial symptoms preceding the clinical manifestation of PSGN typically include sore throat, swollen tonsils covered with a white layer, fever, headache, skin rash, and middle ear infection (Rodriguez-Iturbe & Haas, 2016). However, the patient reports not

experiencing any of these symptoms and sought medical attention already presenting signs of peripheral edema, fluid retention, hypertension, and nephrotic syndrome (detected through urine analysis).

Indeed, the data in this report deviate in several aspects from what is expected in the medical history of a patient with PSGN. Firstly, it is uncommon for a young adult to develop this condition, as it is more commonly observed in children or the elderly (Dhakal et al., 2023). Additionally, the infection did not originate from the commonly affected sites (Rodriguez-Iturbe & Haas, 2026), and the exact latency period between the development of renal disease symptoms and the onset of the endodontic infection could not be determined. However, laboratory and imaging tests used for the clinical diagnosis of PSGN, such as urinalysis, blood samples, serology, and renal biopsy, confirmed the diagnosis. Therefore, the physician had to investigate other possible causes, including infections in the oral cavity.

Referral of the patient to the dentist was essential to confirm the suspicion of the origin of PSGN, as the patient had a compatible history of symptomatic pulpitis that progressed to pulp necrosis in tooth 26, with no other sources of infection in the oral cavity. While the most common type of bacteria associated with PSGN is beta-hemolytic streptococcus group A, other types of streptococcus may also be involved in this condition (Rodriguez-Iturbe & Haas, 2022). A recent study demonstrated that certain strains of *S. mutans* found in pulp tissues and adhered to the root canal (Lima et al., 2020) are capable of invading human endothelial cells and causing bacteremia, contributing to systemic virulence (Abranches et al., 2011). Although microbiological analysis of the root canal content was not performed in this case report due to the high costs involved, it is possible to speculate that a similar mechanism occurred in the patient, triggering antigen-antibody immune complex formation, as confirmed by the immunofluorescence analyses (Fig. 1).

Adults affected by PSGN can develop renal insufficiency, hypertension, and recurrent proteinuria if the underlying infection is left untreated (Satoskar et al., 2020). However, the prognosis becomes very favorable with infection treatment, as can be confirmed in this case report by comparing the tests over time, showing complete remission of the patient's condition, discontinuation of medications, and absence of new disease episodes after endodontic treatment over a period of 2.5 years. Therefore, it is important for healthcare authorities to be aware of endodontic infections as possible causes of PSGN, necessitating a new perspective on this pathology in both children and adults when the etiological factor cannot be clearly determined.

CONCLUSION

Endodontic infection from pulpal necrosis may be the cause of PSGN, and endodontic treatment may help in the rapid remission of disease symptoms, reducing relapses and restoring the patient's quality of life.

FIGURES

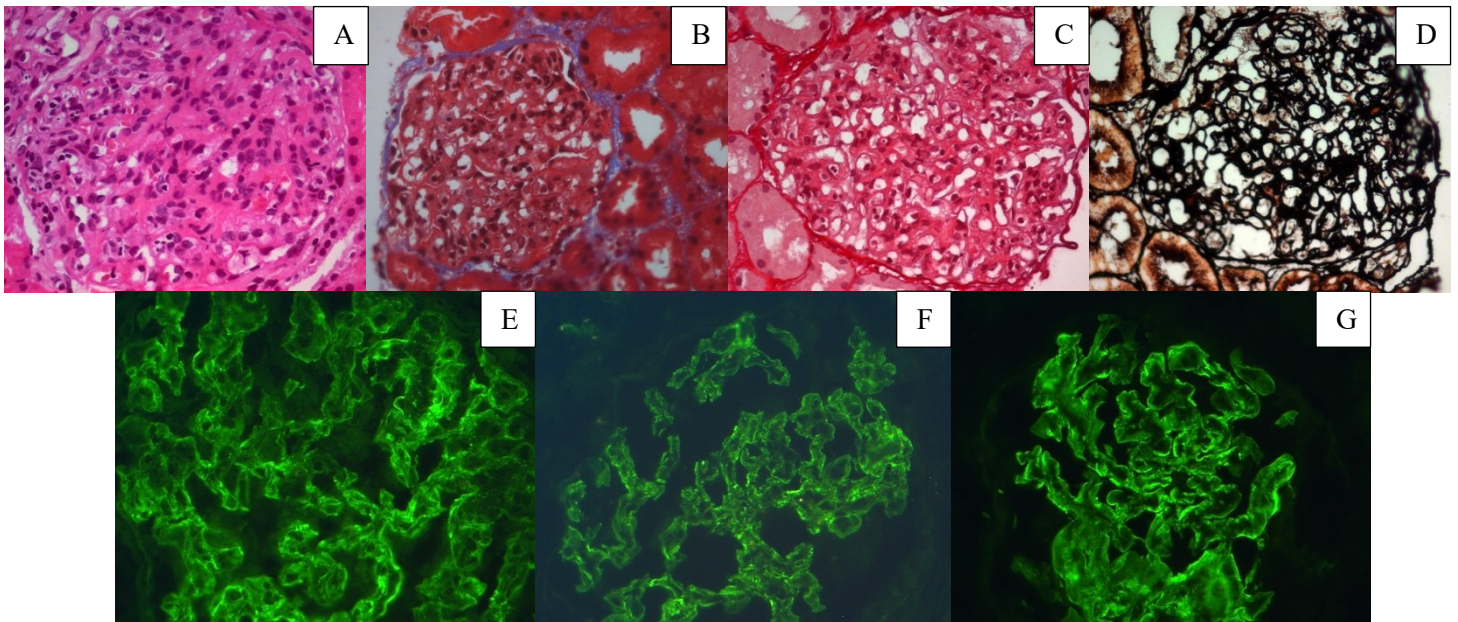


Figure 1: Anatomopathological Examination - Renal Biopsy: Macroscopic findings: A: HE, 40x, 1,0X; B: TM, 40x, 1,0X; C: OS, 40x, 1,0X; D: PAMS, 40x, 1,0X. Immunocomplex/Complement Investigation: A: Anti-IgG serum; B: Anti-C1q serum; C: Anti-C3 serum (direct immunofluorescence microscopy).

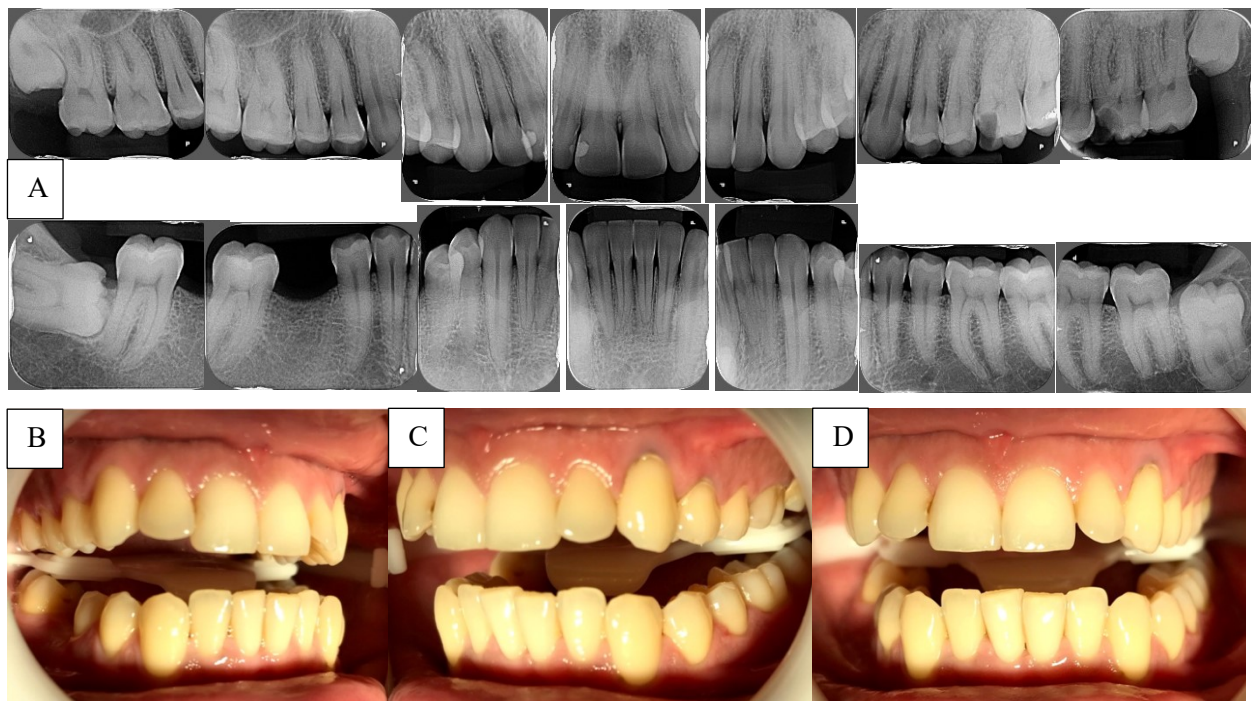


Figure 2: A: Complete Radiographic Examination - Periapical views. Clinical aspect: A: Right side; B: Left side; C: Center.

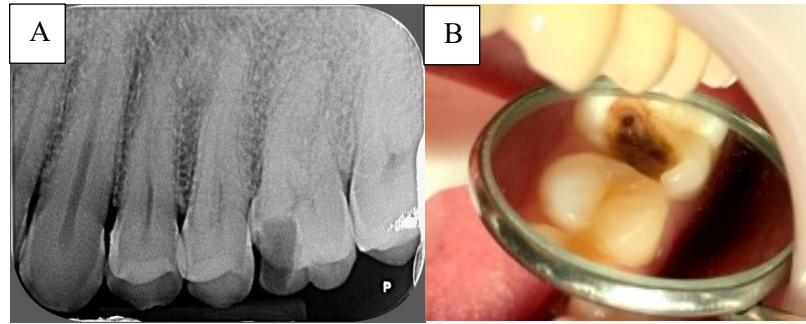


Figure 3: A: Initial radiographic aspect of tooth 26; B: Clinical aspect of tooth 26.

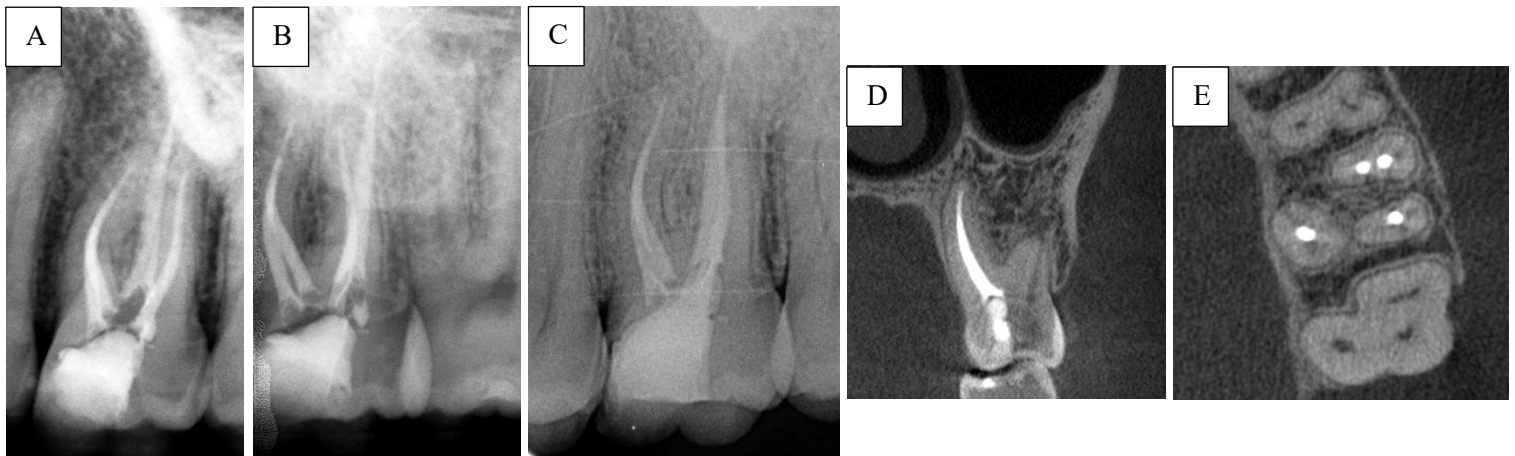


Figure 4: A: Final radiograph of endodontic treatment of tooth 26; B: 30-day follow-up; C: Periapical radiograph at 18 months follow-up; D: Sagittal tomographic sections 18 months follow-up (palatal canal); E: Axial section.

TABLES

Marker	Indicator	10/07/2020	10/25/2020	03/23/2021	08/17/2022
Quantitative PCR	Less than 5 mg/L	7,3 mg/L	-	4,56 mg/L	1,37 mg/L
Neutrophils	1700 a 8000 mm ³	38% - 1.634 mm ³	-	-	-
Segmented Neutrophils	1700 a 8000 mm ³	37% - 1.591 mm ³	-	-	-
Urea	16,6 – 48,5 mg/dL	63 mg/dL	85 mg/dL	39,4 mg/dL	28,3 mg/dL
Creatinine	0,70 a 1,20 mg/dL	2,07 mg/dL	1,54 mg/dL	1,20 mg/dL	0,93 mg/dL
Sodium	135 a 145 mEq/L	-	134 mEq/L	-	-
Glomerular Filtration	66 mL/min/1.63m ²	40 mL/min/1.63m ²	57 mL/min/1.63m ²	90 mL/min/1.63m ²	98 mL/min/1.63m ²
Hemoglobin - Urine	Negative	Positive	-	Negative	Negative
Protein - Urine	Negative	Positive	-	Negative	Negative
Leukocytes - Urine	Until 25.000/mL	38.200/mL	-	23.200/mL	-
Red Blood Cells - Urine	Until 23.000/mL	37.000/mL	-	13.000/mL	-
PCO2 - Blood Gas Analysis	38 a 50 mmHg	34,1 mmHg	51,5 mmHg	-	-
PO2 - Blood Gas Analysis	30 a 50 mmHg	-	26,5 mmHg	-	-
Oxygen Saturation - Blood Gas Analysis	60 a 85%	-	44,5%	-	-
Total CO2 - Blood Gas Analysis	23 a 27 mmol/L	21,8 mmol/L	29,1 mmol/L	-	-
HCO3 - Blood Gas Analysis	24 a 28 mmol/L	20,7 mmol/L	27,5 mmol/L	-	-
Base Excess - Blood Gas Analysis	-2 a +2 mmol/L	- 4 mmol/L	1,9 mmol/L	-	-
Hepatitis C -	Non-reactive	-	Non-reactive	-	-

Anti-HCV					
Hepatitis B - HBsAg	Non-reactive	-	Non-reactive	-	-
Hepatitis B - HBc IgM	Non-reactive	-	Non-reactive	-	-
Hepatitis B - Total HBc	Non-reactive	-	Non-reactive	-	-
Antineutrophil Cytoplasmic Antibodies (ANCA)	Non-reactive	-	Non-reactive	-	-
SM, Anti-Sm Autoantibodies	Negative	-	Negative	-	-
SSA (Ro), Anti-SSA Antibodies	Negative	-	Negative	-	-
Immunoglobulins IgA	63 a 484 mg/dL	-	207,0 mg/dL	-	-

Table 1: Clinical profile of the patient in October 2020, March 2021, and August 2022.

REFERENCES:

1. Abranches J, Miller JH, Martinez AR, et al. The collagen-binding protein Cnm is required for *Streptococcus mutans* adherence to and intracellular invasion of human coronary artery endothelial cells. *Infect Immun*. 2011;79(6):2277-84.
<https://doi.org/10.1128/IAI.00767-10>
2. Arabpour F, Kuzekanani M, Walsh LJ, Mirzaei M. Knowledge, Attitudes and Performance of Iranian Endodontists to Patients with Kidney Diseases. *Eur Endod J*. 2023 Jan;8(1):90-95.
<https://doi.org/10.14744/eej.2022.27247>
3. Chiu CC, Chang YC, Huang RY, Chan JS, Chung CH, Chien WC, Kao YH, Hsiao PJ. Investigation of the Impact of Endodontic Therapy on Survival among Dialysis Patients in Taiwan: A Nationwide Population-Based Cohort Study. *Int J Environ Res Public Health*. 2021 Jan 5;18(1):326.
<https://doi.org/10.3390/ijerph18010326>
4. Cintra LTA, Gomes MS, da Silva CC, Faria FD, Benetti F, Cosme-Silva L, Samuel RO, Pinheiro TN, Estrela C, González AC, Segura-Egea JJ. Evolution of endodontic medicine: a critical narrative review of the interrelationship between endodontics and systemic pathological conditions. *Odontology*. 2021 Oct;109(4):741-769.
<https://doi.org/10.1007/s10266-021-00636-x>
5. Dhakal AK, Shrestha D, Singh SK, Acharya S. Clinical profile of children with acute post-streptococcal glomerulonephritis. *Pediatr Nephrol*. 2023 May 2.
<https://doi.org/10.1007/s00467-023-05982-2>
6. Georgiou AC, van der Waal SV, Buijs MJ, Crielaard W, Zaura E, Brandt BW. Host-microbiome interactions in apical periodontitis: The endodontic microbiome in relation to circulatory immunologic markers. *Int Endod J*. 2023 Jun;56(6):748-764.
<https://doi.org/10.1111/iej.13912>
7. Kreher D, Ernst BLV, Ziebolz D, Haak R, de Fallois J, Ebert T, Schmalz G. Prevalence of Dental Caries in Patients on Renal Replacement Therapy-A Systematic Review. *J Clin Med*. 2023 Feb 14;12(4):1507.
<https://doi.org/10.3390/jcm12041507>
8. Lima AR, Ganguly T, Walker AR, Acosta N, Francisco PA, Pileggi R, Lemos JA, Gomes BPFA, Abranches J. Phenotypic and Genotypic Characterization of *Streptococcus mutans* Strains Isolated from Endodontic Infections. *J Endod*. 2020 Dec;46(12):1876-1883.
<https://doi.org/10.1016/j.joen.2020.09.002>
9. Pinto SW, Sesso R, Vasconcelos E, Watanabe YJ, Pansute AM. Follow-up of patients with epidemic poststreptococcal glomerulonephritis. *Am J Kidney Dis*. 2001 Aug;38(2):249-55.
<https://doi.org/10.1053/ajkd.2001.26083>
10. Rodriguez-Iturbe B, Haas M. Post-Streptococcal Glomerulonephritis. 2016 Feb 10. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations*

[Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016.

11. Rodriguez-Iturbe B, Haas M. Post-Streptococcus pyogenes Glomerulonephritis. 2022 Sep 9 [Updated 2022 Oct 4]. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes: Basic Biology to Clinical Manifestations [Internet]. 2nd edition. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2022 Oct 8. Chapter 27
12. Satoskar AA, Parikh SV, Nadasdy T. Epidemiology, pathogenesis, treatment and outcomes of infection-associated glomerulonephritis. *Nat Rev Nephrol.* 2020 Jan;16(1):32-50. <https://doi.org/10.1038/s41581-019-0178-8>
13. Schmalz G, Patschan S, Patschan D, Ziebolz D. Oral health-related quality of life in adult patients with end-stage kidney diseases undergoing renal replacement therapy - a systematic review. *BMC Nephrol.* 2020 Apr 29;21(1):154. <https://doi.org/10.1186/s12882-020-01824-7>
14. Segura-Egea JJ, Martín-González J, Castellanos-Cosano L. Endodontic medicine: connections between apical periodontitis and systemic diseases. *Int Endod J.* 2015 Oct;48(10):933-51. <https://doi.org/10.1111/iej.12507>
15. Zhu Y, Wang Y, Zhang S, Li J, Li X, Ying Y, Yuan J, Chen K, Deng S, Wang Q. Association of polymicrobial interactions with dental caries development and prevention. *Front Microbiol.* 2023 May 18;14:1162380. <https://doi.org/10.3389/fmicb.2023.1162380>

REFERENCIAS INTRODUÇÃO E REFERENCIAL TEÓRICO

1. Akalin, F. A., Baltacioglu, E., Alver, A., and Karabulut, E. (2007). Lipid peroxidation levels and total oxidant status in serum, saliva and gingival crevicular fluid in patients with chronic periodontitis. *J. Clin. Periodontol.* 34, 558-565. doi: 10.1111/j.1600-051X.2007.01091.x
<https://doi.org/10.1111/j.1600-051X.2007.01091.x>
2. Akalin, F. A., Isiksal, E., Baltacioglu, E., Renda, N., and Karabulut, E. (2008). Superoxide dismutase activity in gingiva in type-2 diabetes mellitus patients with chronic periodontitis. *Arch. Oral Biol.* 53, 44-52. doi: 10.1016/j.archoralbio.2007.07.009
<https://doi.org/10.1016/j.archoralbio.2007.07.009>
3. Georgiou AC, Cornejo Ulloa P, Van Kessel GMH, Crielaard W, Van der Waal SV. Reactive oxygen species can be traced locally and systemically in apical periodontitis: A systematic review. *Arch Oral Biol.* 2021 Sep;129:105167. doi: 10.1016/j.archoralbio.2021.105167. Epub 2021 May 27. PMID: 34126418.
<https://doi.org/10.1016/j.archoralbio.2021.105167>
4. Hernández-Ríos P, Pussinen PJ, Vernal R, Hernández M. Oxidative Stress in the Local and Systemic Events of Apical Periodontitis. *Front Physiol.* 2017 Nov 1;8:869.
<https://doi.org/10.3389/fphys.2017.00869>
5. Inchingolo F, Marrelli M, Annibali S, Cristalli MP, Dipalma G, Inchingolo AD, Palladino A, Inchingolo AM, Gargari M, Tatullo M. Influence of endodontic treatment on systemic oxidative stress. *Int J Med Sci.* 2013 Dec 6;11(1):1-6.
<https://doi.org/10.7150/ijms.6663>
6. Jakovljevic A, Nikolic N, Jacimovic J, Pavlovic O, Milicic B, Beljic-Ivanovic K, Miletic M, Andric M, Milasin J. Prevalence of Apical Periodontitis and Conventional Nonsurgical Root Canal Treatment in General Adult Population: An Updated Systematic Review and Meta-analysis of Cross-sectional Studies Published between 2012 and 2020. *J Endod.* 2020 Oct;46(10):1371-1386.e8. doi: 10.1016/j.joen.2020.07.007. Epub 2020 Jul 14. Erratum in: *J Endod.* 2021 Feb;47(2):336. PMID: 32673634.
<https://doi.org/10.1016/j.joen.2020.07.007>
7. Khalighinejad N, Aminoshariae MR, Aminoshariae A, Kulild JC, Mickel A, Fouad AF. Association between Systemic Diseases and Apical Periodontitis. *J Endod.* 2017 Oct;42(10):1427-34.
<https://doi.org/10.1016/j.joen.2016.07.007>
8. Nathan C, Cunningham-Bussell A. Beyond oxidative stress: an immunologist's guide to reactive oxygen species. *Nat Rev Immunol.* 2013 May;13(5):349-61. doi: 10.1038/nri3423. PMID: 23618831; PMCID: PMC4250048.
<https://doi.org/10.1038/nri3423>
9. Nunes CR, Abreu AMOW. Influência dos radicais livres e envolvimento do processo inflamatório na aterosclerose. *Vertices.* 2012;14(3):53-69

<https://doi.org/10.19180/1809-2667.v14n32012p53-70>

10. Rôças IN, Siqueira JF Jr, Del Aguila CA, Provenzano JC, Guilherme BP, Gonçalves LS. Polymorphism of the CD14 and TLR4 genes and post-treatment apical periodontitis. *J Endod*. 2014 Feb;40(2):168-72. doi: 10.1016/j.joen.2013.10.006. Epub 2013 Nov 13. PMID: 24461398. <https://doi.org/10.1016/j.joen.2013.10.006>

11. Rodriguez-Iturbe B, Haas M. Post-Streptococcus pyogenes Glomerulonephritis. 2022 Sep 9 [Updated 2022 Oct 4]. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations* [Internet]. 2nd edition. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2022 Oct 8. Chapter 27

12. Satoskar AA, Parikh SV, Nadasdy T. Epidemiology, pathogenesis, treatment and outcomes of infection-associated glomerulonephritis. *Nat Rev Nephrol*. 2020 Jan;16(1):32-50. <https://doi.org/10.1038/s41581-019-0178-8>

13. Vengerfeldt V, Mändar R, Saag M, Piir A, Kullisaar T. Oxidative stress in patients with endodontic pathologies. *J Pain Res*. 2017 Aug 24;10:2031-2040. <https://doi.org/10.2147/JPR.S141366>

14. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The Metabolic Signature of Macrophage Responses. *Front Immunol* (2019) 10:1462. doi: 10.3389/fimmu.2019.01462 <https://doi.org/10.3389/fimmu.2019.01462>