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QUAL A INFLUÊNCIA DA DEFICIÊNCIA DE ESTROGÊNIO NA PROGRESSÃO DA PERIODONTITE APICAL? REVISÃO SISTEMÁTICA DE ESTUDOS PRÉ CLÍNICOS

Porto Alegre
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Dissertação de mestrado apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para obtenção do título de Mestre em Clínica Odontológica.

Orientador: Prof. Dr. Marcus Vinícius Reis Só

Porto Alegre

2022

DEDICATÓRIA

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RESUMO

COPAT, BÁRBARA ROMAGNA ROSSETTI. 2022. Qual a influência da deficiência de estrogênio na progressão da periodontite apical? Revisão sistemática de estudos pré clínicos. Dissertação (Pós-Graduação em Odontologia- Clínicas Odontológicas - Endodontia) – Faculdade de Odontologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, 2022.

Objetivos: Esta revisão sistemática teve como objetivo avaliar evidências científicas disponíveis referente à influência da deficiência de estrogênio na progressão de lesões periapicais induzidas. Desenho: Uma estratégia de busca foi realizada nas bases de dados MEDLINE/PubMed, Cochrane Library, Scopus, Web of Science e Grey Literature Report. A avaliação da qualidade foi realizada por meio da SYRCLE RoB Tool e verificada pela ferramenta GRADE (Grading of Recommendations Assessment, Development and Evaluation) adaptada para revisões sistemáticas, incluindo estudos em animais. Resultados: Dos 738 estudos potencialmente relevantes, 12 preencheram os critérios de inclusão. Todos os estudos foram realizados em ratos, sendo a ovariectomia (OVX) o método de indução da deficiência de estrogênio em todos eles. Todos os estudos mostraram impactos negativos da deficiência de estrogênio na progressão da periodontite apical nos grupos OVX. Conclusões: Com uma qualidade de evidência moderada, os resultados indicam que a deficiência de estrogênio prejudica a progressão de lesões periapicais induzidas, agravando o processo de reabsorção óssea. Assim, os clínicos devem estar atentos e devem considerar uma maior atenção para pacientes pós-menopausa e com deficiência de estrogênio durante a prática diária.

Palavras-chave: deficiência de estrogênio, osteoporose, lesão periapical, periodontite apical

ABSTRACT

COPAT, BÁRBARA ROMAGNA ROSSETTI, 2022. What is the influence of estrogen deficiency on the progression of apical periodontitis? Systematic review of preclinical studies. Dissertation (Postgraduate in Dentistry - Dental Clinics - Endodontics) - Faculty of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, 2022.

Objectives: This systematic review aimed to evaluation of the scientific evidence regarding the influence of estrogen deficiency in the progress of induced periapical lesions. Design: A search strategy was performed in the MEDLINE/PubMed, Cochrane Library, Scopus, Web of Science and Grey Literature Report databases. Quality assessmente was performed using the SYRCLE RoB Tool and verified by the GRADE tool (Grading of Recommendations Assessment, Development and Evaluation) adapted for systematic reviews, including animal studies (www.gradepro.org). Results: Of the 738 potentially relevant studies, 12 met the inclusion criteria. All studies were performed in rats, with ovariectomy (OVX) being the method of inducing estrogen deficiency all them. All studies showed negative impacts of estrogens deficiency on the progression of apical periodontitis in the OVX groups. Conclusions: With a moderate quality of evidence, the results indicate that estrogen deficiencie apper to impiar the progression of induced periapical lesions, worsening the bone resorption process. Thus, clinicians should be aware and should consider paying more attention to post-menopausal and estrogen-deficient patients during daily practice.

Keywords: estrogen deficiency, osteoporosis, periapical lesion, apical periodontitis

SUMÁRIO

LISTA DE FIGURAS E TABELAS

Lista de Figuras do Artigo Científico

Lista de Tabelas do Artigo Científico

LISTA DE ABREVIATURAS

SHAM: Grupo controle

OVX: ovariectomia

N-OVX: não ovariectomizadas

Veh: veículo

ZOL: ácido zoledrônico

RLX: raloxifeno

ALN: alendronato

LPS: lipopolissacarídeo

PA- Periodontite apical

Micro CT – Microtomografia computadorizada

1. ANTECEDENTES E JUSTIFICATIVAS

A osteoporose é um importante problema de saúde pública: é uma doença óssea muito comum nos humanos, caracterizada pela redução da massa, deterioração do tecido e rompimento da arquitetura óssea, comprometendo a força do tecido e aumentando o risco de fraturas (Cosman et al. 2015).

Dentro de condições normais, o metabolismo ósseo é caracterizado por um equilíbrio entre a formação e reabsorção óssea. Sendo assim, tanto na deficiência de estrogênio quanto na senescência, ocorre um desequilíbrio na remodelação óssea, o que resulta na redução da massa óssea, caracterizando a osteoporose (Johnson et al. 2002).

O osso é um tecido extremamente ativo (Junqueira & Carneiro 1999). No esqueleto em desenvolvimento, essa atividade é primariamente voltada para o crescimento e a modelação óssea, processos pelos quais o osso atinge sua forma e seu tamanho. No adulto, a atividade metabólica envolve predominantemente a remodelação (Schenk 1994, Katchburian & Arana 1999).

A remodelação óssea é definida como um processo de aposição no qual há remoção localizada do osso antigo (reabsorção) e substituição por osso recentemente formado (Hill & Orth 1998, Meghji 1992). Esse evento continua por toda a vida adulta do indivíduo, sendo responsável pela renovação do esqueleto e mantendo sua integridade anatômica e estrutural (Brown & Josse 2002, Duong & Rodan 2001). A remodelação óssea é um processo fisiológico constante no qual a formação óssea é correspondente à reabsorção, sendo regulada por diversos fatores, como mecanismos regulatórios intracelulares, influência hormonal, fatores locais e externos. Alterações nesse processo podem resultar em diferentes distúrbios, entre eles a osteoporose (Najjar & Kahn 1997).

A osteoporose está relacionada ao metabolismo ósseo, alterando a microarquitetura dos ossos, inclusive os da face. Na osteoporose, os ossos tornam-se menos resistentes, mas a concentração de cálcio na matriz orgânica é normal. Todavia, a quantidade de tecido ósseo é menor, apresentando o osso amplos canais de reabsorção. Essa condição patológica decorre da diminuição na formação óssea, do aumento na reabsorção do osso formado, ou da combinação dos dois fatores (Amadei et al. 2006).

Com a diminuição da secreção de estrógenos na menopausa, tem-se como conseqüência maior atividade metabólica óssea, ou seja, maior ritmo na remodelação óssea (Bandeira et al. 2000). A osteoporose na menopausa é de extrema relevância para a área da saúde (Tanaka et al. 1998), posto que constitui uma das doenças metabólicas ósseas mais comuns e significativas. A diminuição do estrógeno é o fator determinante e responsável pela gênese da osteoporose após a menopausa (Bandeira et al. 2000), sendo a perda óssea mais intensa nos cinco anos que se seguem a ela (Genant et al. 1999). Por isso, essa condição é mais frequente e mais dramática nas mulheres, que chegam a perder cerca de 40% a 50% da massa óssea até o final da vida (Aires 1991). A

osteoporose atinge uma em cada quatro mulheres na menopausa e, após os 65 anos, uma em cada três. A redução da massa óssea após a menopausa apresenta relação primária com o funcionamento ovariano, devido à relação entre o estrógeno e o metabolismo ósseo (Modesto Filho et al. 1996).

Existem evidências clínicas que sugerem uma relação positiva entre a osteoporose e a presença de alterações na massa óssea da cavidade bucal (Horner & Devlin 1998, Pizzo et al. 2010). Tem sido proposto, nessa ordem de ideias, que os índices mandibulares obtidos em radiografias panorâmicas poderiam ser usados no diagnóstico precoce da osteoporose (López-lópez et al. 2011). O papel do dentista se tornaria, assim, sumamente importante, se for levado em consideração que a radiografia panorâmica é realizada rotineiramente na prática odontológica.

Um modelo amplamente utilizado com o intuito de observar as relações entre a osteoporose e as alterações da cavidade bucal é o de estudo em ratos. Os molares de ratos, inclusive seu tecido pulpar, podem ser considerados anatômica, histológica, biológica e fisiologicamente como miniaturas de molares humanos. São, portanto, um modelo de estudo válido para fornecer dados importantes sobre reações de tecidos a questões relacionadas à Odontologia. (Dammaschke et al. 2010)

Com o intuito de elucidar os mecanismos de destruição do osso periapical, estudos concluiram que o modelo animal em ratos é muito semelhante a humanos em relação à microbiologia do canal radicular (Stashenko et al. 1994). Nesse modelo, a remoção bilateral dos ovários é reconhecida na literatura como indutora de deficiência de estrogênio (Wronski et al. 1989). Um grande número de estudos recorreu a essa técnica com o objetivo de induzir a osteoporose, uma vez que é sabido que os baixos níveis de estrogênio são indutores de tal condição. Os grupos controle, nesses estudos, são denominados grupos SHAM, compostos por ratas que passam pelos mesmos passos do procedimento cirúrgico da ovariectomia, porém sem que seja feita a excisão dos ovários (Gilles et al. 1997, Zhang et al. 2007, Xiong et al. 2007, Liu et al. 2010, Gomes-filho et al. 2015, Wayama et al. 2015, Qian et al. 2016, Brasil et al. 2017).

Há estudos na literatura, principalmente em animais, que relacionam a deficiência de estrogênio com a progressão das periodontites apicais (Gomes-filho et al. 2015b, Romualdo et al. 2018, Guan et al. 2020, Lucisano et al. 2020). Essas são decorrentes de uma inflamação do periodonto apical, em consequência à infecção da polpa dentária; a periodontite apical crônica desenvolve um processo inflamatório crônico, caracterizado radiograficamente pela presença de uma área radiolúcida circundando o ápice do dente afetado (Seltzer & Bender 2003).

Lesões periapicais começam como uma infecção bacteriana na polpa dentária e envolvem recrutamento de células inflamatórias, geração de citocinas, elaboração de enzimas líticas, e ativação de osteoclastos, que leva à reabsorção do osso alveolar. Por causa do efeito do estrogênio no processo de reabsorção óssea, uma deficiência de estrogênio pode ser suspeito como um fator agravante na periodontite apical (Amadei et al. 2006).

O estrogênio medeia a proliferação dos osteoclastos, os quais desempenham papéis muito importantes durante a perda óssea alveolar resultante da periodontite apical. No estudo de Guan et al. 2020, foi possível observar que o estrogênio pode agravar a perda óssea alveolar por meio da regulação da proliferação de osteoclastos durante a periodontite apical (PA). No estudo de Lucisano et al. 2020**,** observou-se que em relação ao tamanho da lesão periapical houve diferença estatisticamente significante entre os grupos SHAM e OVX, onde a área da lesão foi maior no grupo ovariectomizado. A área média das lesões periapicais foi 1,0mm^2 para o grupo SHAM e 2,07mm^2 para OVX.

O mesmo foi encontrado no estudo de Romualdo et al. 2018, onde nos grupos em que a PA foi induzida, a varredura por microtomografia computadorizada (Micro-CT) mostrou um volume médio de lesão de 1,80mm^3 no grupo SHAM+PA e 3,88mm^3 no grupo OVX+PA, com uma diferença estatisticamente significativa entre eles. No estudo de Gomes-filho et al. 2015b observou-se que a magnitude da reação inflamatória e da perda óssea foram maiores no grupo Ovarectomia-veículo (OVX-veh) em comparação com os grupos SHAM-veh e Ovarectomia-Raloxifeno (OVX-RLX). Da mesma maneira que as áreas de lesão periapical foram maiores nos grupos OVX-veh ($P<0,001$).

Por isso, o objetivo deste estudo será pesquisar na literatura científica disponível, por meio de uma revisão sistemática, se há influência da deficiência de estrogênio na progressão de lesões periapicais induzidas, e qual a qualidade da evidência dos estudos incluídos.

2. OBJETIVOS

2.1 OBJETIVO GERAL

Realizar uma revisão sistemática avaliando as evidências sobre a influência da deficiência de estrogênio na progressão de lesões periapicais induzidas.

2.2 OBJETIVOS ESPECÍFICOS

Avaliar o risco de viés dos estudos que avaliaram a progressão de lesões periapicais induzidas após tratamento endodôntico em animais com deficiência de estrogênio.

Avaliar a qualidade da evidência científica dos estudos que avaliaram a progressão de lesões periapicais induzidas após tratamento endodôntico em animais com deficiência de estrogênio.

3 ARTIGO CIENTÍFICO

Effects of estrogen deficiency influence on the progression of apical periodontitis. A systematic review of preclinical studies.

Bárbara Romagna Rossetti Copat, Angélica Fensterseifer Lemos, Bruna Barcelos Só, Theodoro Weissheimer, Manoela Domingues Martins, Marcus Vinicius Reis Só.

INTRODUCTION

Osteoporosis is a common systemic skeletal disease. In 2021, its worldwide prevalence was of 18.3%. From these, 23.1% were women, and 11.7% were men (Salari et al. 2021). The pathophysiology is characterized by an elevated osteoclastic activity that prevails over the osteoblastic activity (Rachner et al. 2011). Clinically, osteoporosis is characterized by low bone mass, degradation of bone tissue and alteration of bone architecture, decreased bone strength and increased risk of bone fracture (Cosman et al. 2014).

Risk factors for osteoporosis involve aging process, smoking, genetics, alcohol consumption, low calcium intake, long-term glucocorticoid therapies and systemic diseases (Marcucci & Brandi 2015, Curtis et al. 2016). Nevertheless, the leading risk factor for osteoporosis is estrogen deficiency, especially in postmenopausal women, caused by the decrease in ovarian function (Li & Wang 2018).

Estrogen plays important roles in a wide range of functions during bone homeostasis. Among estrogen main functions are regulating cytokines associated to bone resorption stimulus; stimulating the functioning and differentiation of osteoclasts; inhibiting activity and differentiation of osteoclasts through cellular effects; inhibiting RANKL production by mesenchymal stem cells, osteoblasts, and osteocytes (Curtis et al. 2016, Eastell et al. 2016, Streicher et al. 2017). A deficiency in this hormone may promote an unbalance in bone turnover, favouring increased bone resorption (Cheng et al. 2022).

Apical periodontitis (AP) is a highly prevalent inflammatory process (Tibúrcio-Machado et al. 2021) of the periradicular tissues, that occur as a host defense response to pathogens and their toxins occupying the root canal system (Kakehashi et al. 1965, Nair 2004, Ricucci & Siqueira 2010). The mechanism involves recruitment of inflammatory cells, generation of cytokines, elaboration of lytic enzymes and activation of osteoclasts, leading to alveolar bone resorption, and to the formation of a granulomatous tissue and a dense layer of polymorphonuclear leukocytes (Graunaite et al. 2012, Galler et al. 2021); radiographically depicted as a periapical radiolucency.

Among the generated cytokines, studies reported that interleukin-1 (IL-1) is produced by several cells and mediated by several other cytokines present in the periapical inflammation (Graunaite et al. 2012). Its local effects comprise the enhancement of leukocyte adhesion to endothelial walls, stimulation of lymphocytes, potentiation of neutrophils, activation of the production of prostaglandins and proteolytic enzymes, enhancement of bone resorption, inhibition of bone formation (Nair 2004). Since both osteoporosis and AP are characterized by the occurrence of of a osteolysis resulted from inflammation (Pizzo et al. 2010), it is possible to infer that osteoporosis has the potential to aggravate apical periodontitis.

So far, there is limited scientific information derived from clinical studies indicating that osteoporotic patients appear to have a higher risk of presenting AP in comparison to non-osteoporotic patients (López-López et al. 2015, Katz & Rotstein 2021). However, mainly due to ethical considerations, there are no clinical studies evaluating the influence of osteoporosis or estrogen deficiency in AP progression. To overcome this limitation, an increased number of studies aiming to investigate this correlation have been performed in animal models, mainly performed in rats (Xiong et al. 2007, Liu et al. 2010, Wayama et al. 2015, Qian et al. 2016, Brasil et al. 2017). In these experimental studies, the methodology involves the bilateral removal of the animals' ovaries which will lead to an estrogen deficiency, and the consequent osteoporotic disease (Wronski et al. 1989). In terms of endodontic procedures, pulp exposure (Kakehashi et al. 1965) or root canal system exposure (Paula-Silva et al. 2020) to the oral cavity is performed, inducing, then, the AP.

Mainly due to the epidemiological scenario of osteoporosis, and apical periodontitis, it is necessary to evaluate the available evidence on the influence of estrogen deficiency in AP progression. For this reason, this systematic review aimed to answer the following question: Does estrogen deficiency influence on the progression of apical periodontitis?

MATERIAL AND METHODS

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Page et al. 2020), and a protocol was registered in the PROSPERO database (CRD42021269555).

Search strategy

Electronic searches were independently performed by two examiners (B.R.R.C. and A.F.L.) in the following electronic databases: MEDLINE/PubMed, Cochrane Library, Scopus, Web of Science, EMBASE, and Grey Literature Report (grey literature search). Database search was conducted up to April 2022, without year or language restriction. The electronic search strategy employed the most cited descriptors in this field according to previous publications, combining Medical Subject Heading (MeSH) terms and text words (tw.). The Boolean operators "AND" and "OR" were applied to combine the terms and create a search strategy. The search strategies for each database and the studies retrieved are summarised in Supplementary Table 1. Additional manual search of the reference lists of the selected studies was performed. All articles selected were imported into the Mendeley© (Mendeley Ltd, London, United Kingdom) reference manager to catalogue the references and facilitate the exclusion of duplicates.

Eligibility criteria

The eligibility criteria were selected according to the PICOS strategy (Maia & Antonio 2012, Moher et al. 2015, Page et al. 2020).

•Population (P): animals with estrogen deficiency;

•Intervention (I): induction of apical periodontitis;

•Comparison (C): animals without estrogen deficiency (control group or sham surgery)

•Outcome (O): bidimensional and/or tridimensional measures of apical periodontitis progression;

•Study design (S): studies in animal models.

Studies in which animals presented other systemic diseases; studies that evaluated other oral diseases (i.e., periodontitis); studies that used in male animals; systematic reviews with and without meta-analysis, reviews, letters, opinion articles, conference abstracts, case reports, and case series were excluded.

Selection of the studies

Study selection was performed by two independent authors (B.R.R.C. and A.F.L.), who conducted the database search, removed duplicates and screened titles and abstracts. If title and abstract were not sufficient to determine inclusion, the full text was read for a final decision. After that, potentially eligible studies were then read for full-text assessment using the PICOS criteria. Divergences between reviewers were solved by discussing with a third author (M.V.R.S.).

Data extraction

Two authors (B.R.R.C. and A.F.L.) performed data extraction independently. Disagreements were solved by discussing with a third author (M.V.R.S.). Data extracted from the studies included were the following: authors' names, year of publication, animal model, sample size, investigated groups, method to induce estrogen deficiency, drug therapy, method to induce apical periodontitis, teeth evaluated, method to assess apical periodontitis progression, time of outcome assessment, outcomes, main findings. In case of missing information, the authors were contacted three times by e-mail at an interval of one week.

Qualitative assessment

Quality assessment of the selected studies was performed using the Systematic Review Centre for Laboratory Animal Experimentation Risk of Bias (SYRCLE RoB Tool). This tool was specifically developed for the risk of bias assessment in animal research, based on the Cochrane Collaboration (Hooijmans et al. 2014). The SYRCLE RoB Tool consists of 10 domains, classified as the sort of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. For each domain, the studies received a score of "high risk of bias"

(when the study does not meet one or more criteria); "unclear risk of bias" (when the study does not present the necessary data or partly meet one or more criteria), or "low risk of bias" (when all the requirements were met).

Certainty of evidence

The certainty of the evidence of the included studies was assessed using an adapted methodology for preclinical animal studies of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (Hooijmans et al. 2018). The GRADE tool has five domains that can be downgraded and reduce the quality of the evidence (GRADE Working Group, 2004). The following domains were included in this assessment: (1) Risk of bias; (2) Inconsistency; (3) Indirectness; (4) Imprecision; (5) Other considerations.

RESULTS

Study selection

Initial screening of databases resulted in 738 studies, with 325 excluded by duplicates removal. From the analysis of the titles and abstracts of the 413 eligible papers, eighteen studies (Gilles et al. 1997, Xiong et al. 2007, Zhang et al. 2007, Liu et al. 2010, Gomes-Filho et al. 2015a, 2015b, Wayama et al. 2015, Antonela et al. 2016, Qian et al. 2016, 2020, Brasil et al. 2017, Rao et al. 2017, 2019, Youssef & Stashenko 2017, Romualdo et al. 2018, Guan et al. 2020, Silva et al. 2020, Lucisano et al. 2021) were selected for full-text reading.

After full-text reading, six studies were excluded, with three being excluded for not presenting a control group (Antonela et al. 2016, Rao et al. 2017, 2019), and three for presenting outcomes other than apical periodontitis progression (Zhang et al. 2007, Gomes-Filho et al. 2015b, Youssef & Stashenko 2017). Finally, twelve studies were included in the present systematic review (Gilles et al. 1997, Xiong et al. 2007, Liu et al. 2010, Gomes-Filho et al. 2015a, Wayama et al. 2015, Qian et al. 2016, 2020, Brasil et al. 2017, Romualdo et al. 2018, Guan et al. 2020, Silva et al. 2020, Lucisano et al. 2021).

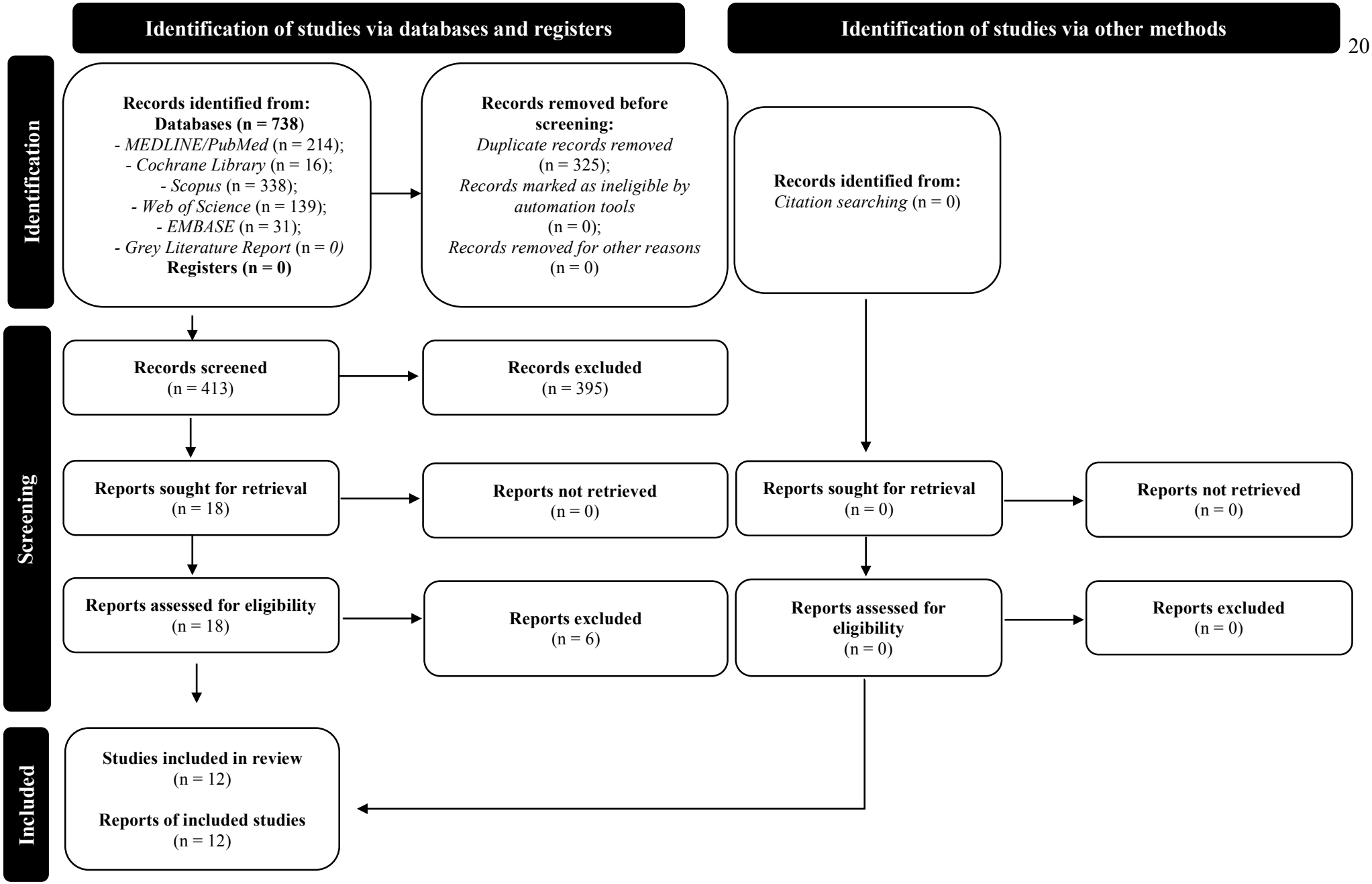

Figure 1 presents the flow diagram of the search strategy.

Data extraction

Table 1 presents the characteristics and main findings of the included studies.

All studies used rat-models and performed bilateral ovariectomies for induction of estrogen deficiency. Furthermore, most studies induced apical periodontitis by exposing the dental pulp to the oral cavity (Xiong et al. 2007, Liut et al. 2010, Gomes-Filho et al. 2015a, Wayama et al. 2015, Qian et al. 2016, Brasil et al. 2017, Romualdo et al. 2018, Guan et al. 2020, Qian et al. 2020); while two studies performed pulpectomies (Silva et al. 2020, Lucisano et al. 2021); and one study performed pulpectomy and intracanal injection with bone resorbing factors (Gilles et al. 1997).

Regarding teeth evaluated, most studies performed the evaluations on mandibular first molars, with only two studies evaluating mandibular and maxillary first molars (Romualdo et al. 2018, Silva et al. 2020). In addition, most studies assessed the investigated outcomes after 21 days only (Xiong et al. 2007, Liu et al. 2010, Romualdo et al. 2018, Qian et al. 2020, Silva et al. 2020, Lucisano et al. 2021); while time of outcome assessment from other studies ranged from 0 to forty days.

As for the main findings, all included studies concluded that estrogen deficiency increased the progression of apical periodontitis. Furthermore, seven studies evaluated the effects of drug therapies to prevent or treat osteoporosis on the progression of apical periodontitis in ovariectomized rats (Xiong et al. 2007, Liu et al. 2010, Gomes-Filho et al. 2015a, Wayama et al. 2015, Qian et al. 2016, 2020, Silva et al. 2020), and concluded that the tested drugs had a protective effect on the bone tissue, restraining the progression of bone destruction in apical periodontitis.

Qualitative assessment

Risk of bias assessment of the included studies is displayed in **Figure 2** (McGuinness & Higgins, 2020).

Considering all domains evaluated by the SYRCLE's RoB tool, four ("Allocation concealment", "Random housing", "Blinding of participants", and "Random outcome

assessment") were classified as a high risk of bias for all studies. In the domain "Random sequence generation", six studies (Gilles et al. 1997, Xiong et al. 2007, Gomes-Filho et al. 2015a, Wayama et al. 2015, Brasil et al. 2017, Romualdo et al. 2018) had a high risk of bias; and six studies (Liu et al. 2010, Qian et al. 2016, 2020, Guan et al. 2020, Silva et al. 2020, Lucisano et al. 2021) had an unclear risk of bias. In the domain "Baseline characteristics", seven studies (Gilles et al. 1997, Xiong et al. 2007, Gomes-Filho et al. 2015a, Wayama et al. 2015, Romualdo et al. 2018, Silva et al. 2020, Lucisano et al. 2021) had an unclear risk of bias; while the other studies had a low risk of bias. In the domain "Blinding of outcome assessment", four studies (Gilles et al. 1997, Wayama et al. 2015, Romualdo et al. 2018, Silva et al. 2020) had a high risk of bias; two studies (Gomes-Filho et al. 2015a, Lucisano et al. 2021) had an unclear risk of bias; and the remaining studies had a low risk of bias. Finally, in "Incomplete outcome data", "Selective reporting" and "Other bias" all studies had a low risk of bias".

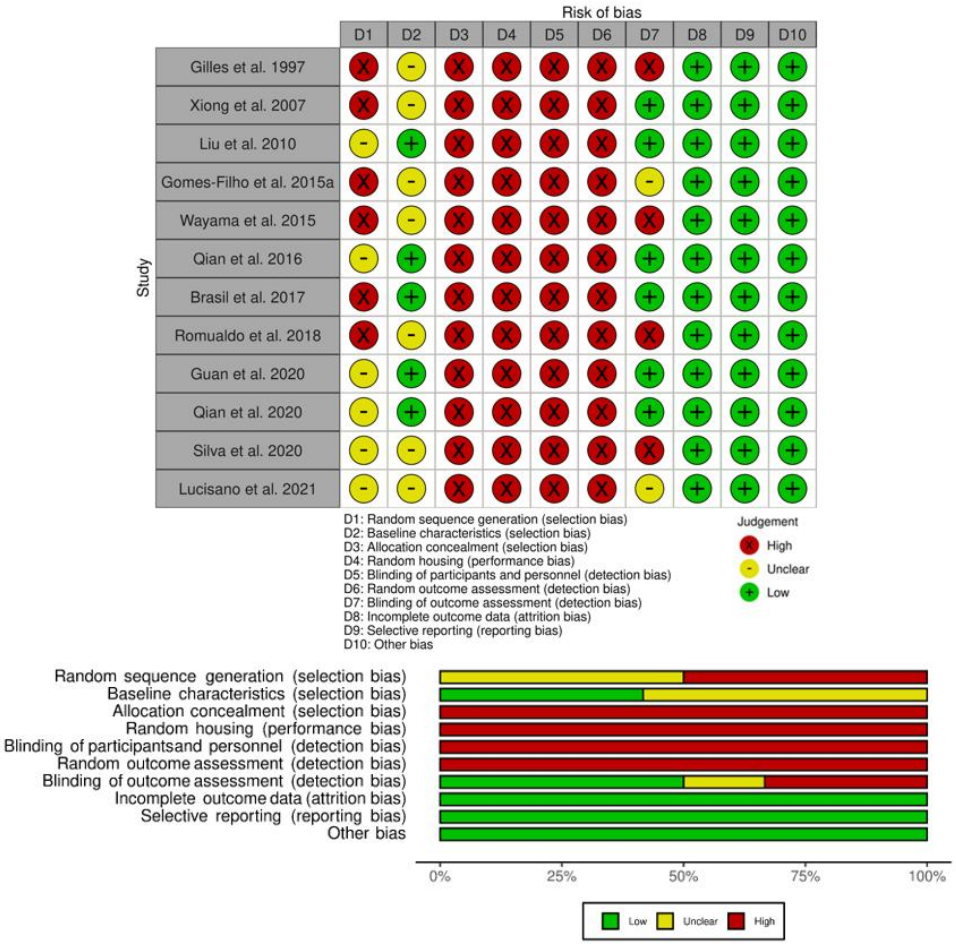

Figure 2 Risk of bias assessment of the included studies

Certainty of evidence

Results of the GRADE assessment are summarized in **Table 2**.

According to the recommendations for assessment of the certainty of evidence from preclinical animal studies (Hooijmans et al. 2018), initial certainty is high. “Risk of bias” received the ‘very serious’ classification, and for this reason the overall certainty was downgraded. “Inconsistency”, “Indirectness” and “Imprecision” were classified as ‘not serious’. The studies were upgraded in the other domains because a strong association was verified. Therefore, the overall certainty of evidence for the included studies was moderate.

DISCUSSION

Despite being a local inflammatory disease, recent evidence point out correlations between systemic diseases and apical periodontitis (Segura-Egea et al. 2015, Aminoshariae et al. 2017, Jakovljevic et al. 2020, Nagendrababu et al. 2020). Due to the growing epidemiological scenario of osteoporosis and apical periodontitis (Salari et al. 2021, Tibúrcio-Machado et al. 2021), studies that seek to elucidate a possible relationship between both conditions are necessary. So far, clinical studies point for a higher risk of osteoporotic patients to present apical periodontitis (López-López et al. 2015, Katz & Rotstein 2021). In addition, evidence for a possible relationship between estrogen deficiency, relating to an osteoporotic condition, and its influence on the progression of apical periodontitis are available from several preclinical studies in animal models. For this reason, a systematic review that evaluate the quality of these studies is warranted.

Therefore, the present review performed a systematic search in six electronic databases, looking for preclinical studies that evaluated the progression of apical periodontitis in animal models with induced estrogen deficiency. Findings of all studies demonstrated that an hypoestrogenic condition can favour an increased progression of apical periodontitis, leading to an increased local bone resorption.

These findings can be explained by the fact that hypoestrogenic conditions exacerbates the expression of several proinflammatory cytokines, such as interleukin-1 (IL-1) and interleukin-

6 (IL-6), and tumour necrosis factors, found in increased levels in ovariectomized rats (Romualdo et al. 2018, Guan et al. 2020, Qian et al. 2020, Silva et al. 2020) and post-menopausal women (Jeffcoat et al. 2000). In addition, estrogen deficiency can induce alteration on the oral microbiota, by increasing the number of bacteria in the oral saliva, which could also be responsible for the development of larger periapical lesions (Lucisano et al. 2021).

It is important to emphasize that the estrogen mecanism is related to the alterations in regulatory modulating factors of osteoclastogenesis, and not to a direct action on osteoclasts (Vanderschueren et al. 2004). Thus, the estrogen deficiency causes an imbalance in bone remodelling process, exacerbating the resorptive process, inducing an increased number of active osteoclastic cells, consequently generating periapical lesions of larger sizes (Gomes-Filho et al. 2015a).

Even though the current scientific evidence is from animal studies, the ovariectomized rat model is known to result in bone loss similarly to those in post-menopausal women (Kalu 1991), directly related to estrogen deficiency and the development of osteoporosis. This allows the performance of studies evaluating estrogen deficiency on several aspects (Thompson et al. 1995).

Additionally, some studies evaluated the effects of drug therapies to prevent or treat osteoporosis on the progression of apical periodontitis (Xiong et al. 2007, Liu et al. 2010, Gomes-Filho et al. 2015a, Wayama et al. 2015, Qian et al. 2016, 2020, Silva et al. 2020). Among these drugs, bisphosphonates – alendronate (Xiong et al. 2007, Silva et al. 2020) and zoledronic acid (Wayama et al. 2015), a gonadotrophin-releasing hormone analogue – leuprorelin (Liu et al. 2010, Qian et al. 2016, 2020), and an oral selective estrogen receptor modulator – raloxifene (Gomes-Filho et al. 20015a), were tested. Regardless of the tested drugs, all studies concluded that their administration had a protective effect on bone tissue, reducing its resorptive process during induced apical periodontitis (Xiong et al. 2007, Liu et al. 2010, Gomes-Filho et al. 2015a, Wayama et al. 2015, Qian et al. 2016, 2020, Silva et al. 2020). Therefore, despite the differences in the mechanism of action of these substances, it is possible to infer that these present a positive

effect modulating the osteoclasts activity during apical periodontitis (Xiong et al. 2007, Liu et al. 2010, Gomes-Filho et al. 2015a, Wayama et al. 2015, Qian et al. 2016, 2020, Silva et al. 2020).

Regarding the risk of bias assessment of the included studies, several drawbacks were observed. None of the included studies informed the procedures used to conceal the allocation and did not report the methods to randomly house the animals. Furthermore, they also did not address the approach to blind researchers, neither whether the animals were selected at random for outcome assessment. For these reasons, in 'Allocation concealment', 'Random housing', 'Blinding of participants and personnel', and 'Random outcome assessment' domains, a high risk of bias. Was attributed to all studies. Additionally, six studies did not inform if the animals were randomly allocated to each experimental group (Gilles et al. 1997, Xiong et al. 2007, Gomes-Filho et al. 2015a, Wayama et al. 2015, Brasil et al. 2017, Romualdo et al. 2018), and six studies informed that animals were randomized, but did not describe how this randomization was performed (Liu et al. 2010, Qian et al. 2016, 2020, Guan et al. 2020, Silva et al. 2020, Lucisano et al. 2021). Therefore, a high and unclear risk of bias in the domain 'Random sequence generation', respectively was respectively attributed to these studies. In the domain 'Baseline characteristics', authors should report the characteristics of animals of the study, including information on sex, age, weight and timing of disease induction. Seven studies (Gilles et al. 1997, Xiong et al. 2007, Gomes-Filho et al. 2015a, Wayama et al. 2015, Romualdo et al. 2018, Silva et al. 2020, Lucisano et al. 2021) were classified with an unclear risk of bias, as they partially informed these characteristics. Finally, in the domain 'Blinding of outcome assessment', four studies had a high risk of bias (Gilles et al. 1997, Wayama et al. 2015, Romualdo et al. 2018, Silva et al. 2020), and two had an unclear risk of bias (Gomes-Filho et al. 2015a, Lucisano et al. 2021). A high risk of bias was attributed when no blinding was performed in none of the investigated outcomes; and an unclear risk of bias was when blinding was performed in only some but not all the investigated outcomes.

According to the guidelines for assessing the certainty of evidence in preclinical animal studies (Hooijmans et al. 2018), the initial certainty is classified as high. Mainly due to the limitations presented by the risk of bias assessment, the domain "Risk of bias" was classified as

'very serious' and the initial certainty was downgraded in two. No limitations were verified in the domains "Imprecision", "Indirectness" and "Inconsistency". Finally, since all studies concluded that estrogen deficiency increased the progression of apical periodontitis, a 'strong association' was verified, upgrading in one the certainty of evidence in the domain "Other considerations". Therefore, in this systematic review, the GRADE analysis demonstrated a moderate certainty of evidence.

As previously mentioned, the included studies demonstrated several limitations regarding randomization, blinding and description of baseline characteristics. This should be considered at evaluating the information presented hereby and for future studies on the same subject. In addition, none of the studies has evaluated the effects of endodontic treatment on periapical repair in estrogen deficient rat-models. Thus, despite there seem to be a correlation between estrogen deficiency and increased apical periodontitis progression, it is not possible to determine whether this condition affects periapical healing process after endodontic treatment. Secondly, no study compared the effects of the tested drug therapies between them, making impossible to determine the best adjunct treatment modality when apical periodontitis treatment is necessary. Further studies are needed to elucidate these topics.

Overall, in the absence of better-quality studies, this systematic review demonstrated that an hypoestrogenic condition can aggravate the apical periodontitis progression. Thus, clinicians should be aware and must consider a greater attention for post-menopausal and estrogen deficient patients during daily practice.

CONCLUSION

With a moderate quality of evidence, it may be concluded that estrogen deficiency influence the apical periodontitis progression, by aggravating the bone resorptive process. Additionally, drug therapies to prevent or treat osteoporosis seems to play a protective role on bone tissue during apical periodontitis.

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TABLES

Table 1. Characteristics of the included studies.

Authors (Year of publication)	Animal model (Sample size)	Investigated groups (Samples per group)	Method to induce estrogen deficiency	Adjunct drug therapy	Method to induce apical periodontitis	Teeth evaluated	Method to assess apical periodontitis progression	Time of outcome assessment	Outcomes	Main findings
Gilles et al. (1997)	Female rats (N = NR)	Control (N-OVX; n=NR); Ovariectomy (OVX; n=NR)	Bilateral ovariectomy	NA	Pulpectomy and intracanal injection of bone resorbing factors	Mandibular first molars	Radiographic analysis of periapical lesion area (in mm^2)	After 3 days	Significant bone resorption in OVX rats compared to N-OVX rats	Estrogen deficiency resulted in increased bone resorption in apical periodontitis
Xiong et al. (2007)	Female rats (N = 40)	Sham surgery (n = 10); Sham surgery + pulpal exposure (n = 10); OVX + pulpal exposure + vehicle (n = 10); OVX + pulpal exposure + alendronate (n = 10)	Bilateral ovariectomy	Alendronate (ALN)	Pulpal exposure	Mandibular first molars	Radiographic and histologic analysis of periapical lesion area (both in mm^2)	After 21 days	Radiographic and histological analyses showed larger periapical lesion size in the OVX + vehicle group; Daily alendronate administration reduced the bone loss in the periapical region;	Estrogen deficiency enhanced bone loss in apical periodontitis; Alendronate therapy had a protective effect

Liu et al. (2010)	Female rats (N = 27)	Sham surgery (n = 6); Sham surgery + pulpal exposure (n = 6); OVX + pulpal exposure (n = 7); OVX + pulpal exposure + leuprorelin (n = 8)	Bilateral ovariectomy	Leuproleri n (LE)	Pulpal exposure	Mandibular first molars	Radiographic and histologic analysis of periapical lesion area (both in mm^2)	After 21 days	Radiographic analyses showed an increased bone loss for both OVX groups, without differences between them; Histologic analyses also presented an increased bone loss for both OVX groups, with OVX + LE showing a lower bone loss compared to OVX only	Estrogen deficiency enhanced bone loss in apical periodonti-tis; Leuprolerin therapy had a protective effect

Gomes-Filho et al. (2015a)	Female rats (N = 48)	Sham surgery + pulpal exposure + vehicle 7d (n = 8); Sham surgery + pulpal exposure + vehicle 30d (n = 8); OVX + pulpal exposure + vehicle 7d (n = 8); OVX + pulpal exposure + vehicle 30d (n = 8); OVX + pulpal exposure + raloxifene 7d (n = 8); OVX + pulpal exposure + raloxifene 30d (n = 8)	Bilateral ovariectomy	Raloxifene (RLX)	Pulpal exposure	Mandibular first molars	Radiographic density and histometric analysis of periapical lesion area (both in mm^2)	After 7 and 30 days	Radiographic density of periapical lesions after 30 days was lower than after 7 days, without differences between groups; Periapical lesion area was larger in OVX + vehicle groups, when compared to the other groups; Periapical lesion area in OVX + RLX was similar to Sham surgery + vehicle groups	Estrogen deficiency potentiated the progression of periapical lesions; Raloxifene reversed this condition

Wayama et al. (2015)	Female rats (N = 40)	Sham surgery + pulpal exposure + vehicle 7d (n = 5); Sham surgery + pulpal exposure + vehicle 30d (n = 5); Sham surgery + pulpal exposure + zoledronic acid 7d (n = 5); Sham surgery + pulpal exposure + zoledronic acid 30d (n = 5) OVX + pulpal exposure + vehicle 7d (n = 5); OVX + pulpal exposure + vehicle 30d (n = 5); OVX + pulpal exposure + zoledronic acid 7d (n = 5); OVX + pulpal exposure +	Bilateral ovariectomy	Zoledronic acid (ZOL)	Pulpal exposure	Mandibular first molars	Micro-computed tomography (Micro-CT; in mm) and histometric (in mm^2) analysis of periapical lesion area	After 7 and 30 days	Micro-CT sections showed that at both times, bone loss in all sections was higher in the OVX + vehicle group; Bone loss in the coronal and axial sections was similar in the Sham + vehicle, Sham + ZOL, and OVX + ZOL, at both times; On day 30, Sham + ZOL group had less bone loss in the sagittal section than the other groups; Histometric analysis showed that OVX + vehicle had the greater periapical lesions; Sham + vehicle and OVX + ZOL had similar lesion areas; and SHAM + ZOL had the smallest lesion areas	Hypoestrogenic condition aggravated the progression of periapical lesions; Zoledronic acid contained bone destruction of periapical lesions

zoledronic acid 30d (n = 5)

Qian et al. (2016)	Female rats (N = 90)	Sham surgery + pulpal exposure + vehicle (n = 15); OVX + pulpal exposure + vehicle (n = 15); OVX + pulpal exposure + leuprolerin (n = 15); OVX + pulpal exposure + leuprolerin + luteinizing hormone (n = 15); OVX + pulpal exposure + leuprolerin + luteinizing hormone + follicle-stimulating hormone (n = 15); OVX + pulpal exposure + follicle-stimulating hormone (n = 15)	Bilateral ovariectomy	LE; Follicle-stimulating hormone (FHS); Luteinizing hormone (LH)	Pulpal exposure	Mandibular first molars	Histologic analysis of periapical lesion area (in mm^2)	After 7, 14 and 21 days	OVX groups exhibited increases in bone loss of periapical lesions compared to the Sham groups, which were reversed by administration of LE or LE + LH; Bone loss of periapical lesions were increased following administration of FSH, when compared to the Sham and OVX groups	Estrogen deficiency resulted in increased bone loss; Administration of leuprolerin, and leuprolerin + luteinizing hormone reversed this condition; Follicle-stimulating hormone increased bone loss

Brasil et al. (2017)	Female rats (N = 24)	Sham surgery + pulpal exposure 21d (n = 6); Sham surgery + pulpal exposure 40d (n = 6); OVX + pulpal exposure 21d (n = 6); OVX + pulpal exposure 40d (n = 6)	Bilateral ovariectomy	NA	Pulpal exposure	Mandibular first molars	Radiographic analysis of periapical lesion area (in pixels)	After 21 and 40 days	Periapical lesion areas were higher for OVX groups at both times when compared to the Sham groups, but only significant for comparisons involving OVX 40d and Sham 21d and 40d	Long periods of estrogen deficiency can influence the progression of apical periodontitis
Romualdo et al. (2018)	Female rats (N = 20)	Sham surgery (n = 5); Sham surgery + pulpal exposure (n = 5); OVX (n = 5); OVX + pulpal exposure (n = 5)	Bilateral ovariectomy	NA	Pulpal exposure	Mandibular and maxillary first molars	Micro-CT of periapical lesion area (in mm^3)	After 21 days	Micro–CT imaging showed a greater periapical lesion mean volume in OVX compared with sham animals	Hypoestrogenic conditions can aggravate the inflammatory process of periapical lesions
Guan et al. (2020)	Female rats (N = 50)	Sham surgery + pulpal exposure (n = 25); OVX + pulpal exposure (n = 25)	Bilateral ovariectomy	NA	Pulpal exposure	Mandibular first molars	Radiographic and histologic analysis of periapical lesion area (both in mm^2)	After 0, 7, 14, 21 and 28 days	No bone loss was observed at day 0 in both groups; Bone loss was significantly increased in the OVX group over time, when compared to the Sham groups	Estrogen deficiency can influence the progression of apical periodontitis

Qian et al. (2020)	Female rats (N = 30)	Sham surgery + pulpal exposure + vehicle (n = 10); OVX + pulpal exposure + vehicle (n = 10); OVX + pulpal exposure + LE (n = 10)	Bilateral ovariectomy	LE	Pulpal exposure	Mandibular first molars	Micro-CT (in mm^3) and histologic analyses (in mm^2) of the periapical lesion volume and area, respectively	After 21 days	Micro-CT analysis revealed that the periapical lesion volumes were larger in the OVX groups than in the Sham group, where their growth was prevented by LE treatment; Histologic analysis showed that periapical lesions in the OVX groups were increased compared with the Sham group, and were reversed by the administration of LE	Increased bone loss can be observed as a result of estrogen deficiency; Leuprolerin administration resulted in a decrease in the inflammatory process
Silva et al. (2020)	Female rats (N = 25)	Sham surgery + pulpectomy (n = 5); OVX + pulpectomy (n = 10); OVX + pulpectomy + ALN (n = 10)	Bilateral ovariectomy	ALN	Pulpectomy	Mandibular and maxillary first molars	Fluorescence microscopy of the periapical lesion area (in mm^2)	After 21 days	Periapical lesion area of OVX group was greater than the lesion of the Sham and OVX + ALN groups; No differences were found between the Sham and OVX + ALN groups	Estrogen deficiency increased the periapical lesion progresson; Alendronate had a protective effect on the bone tissue against the progression of periapical lesions

Lucisano et al. (2021)	Female rats (N = 36)	Sham surgery (n = 9); Sham surgery + periapical lesion (n = 9); OVX (n = 9); OVX + periapical lesion (n = 9)	Bilateral ovariectomy	NA	Pulpectomy	Mandibular first molars	Fluorescence microscopy of the periapical lesion area (in mm2)	After 21 days	Periapical lesion area was higher for the OVX + periapical lesion group, compared to the Sham + periapical group	Hypoestrogenic conditions can influence the progession of periapical lesions

Legend: **ALN**: alendronate; **NR**: not reported; **NA**: not applicable; **OVX:** ovariectomy; **RLX**: raloxifene; **ZOL**: zoledronic acid; **Micro-CT**: micro-computed tomography; **LE**: leuprolerin; **FHS**: follicle-stimulating hormone; **LH**: luteinizing hormone.

Table 2. Certainty of the evidence from the included studies according to the GRADE approach for preclinical animal studies.

Certainty assessment						
Number of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Overall certainty of evidence**
12 studies	Very serious [a]	Not serious	Not serious	Not serious	Strong association	⊕⊕⊕◯ MODERATE

a. Several domains had studies with an unclear or high risk of bias.

5 CONSIDERAÇÕES FINAIS

O presente estudo apresentou uma revisão sistemática da literatura abordando a influência da deficiência do estrogênio na progressão da periodontite apical. Foram encontradas algumas limitações que precisam ser reconhecidas. Em primeiro lugar, os estudos incluídos são bastante heterogêneos quanto a metodologia utilizada, o que não permitiu a realização de uma metanálise, pois as questões e os escores são medidos de diferentes maneiras.

Foi possível verificar à falta de informações referentes à alocação dos animais, cegamento dos cuidadores e processos de randomização na formação dos grupos de estudos. Além disso, observou-se em alguns estudos que no grupo controle continham também animais submetidos à administração de fármacos para controle hormonal.

Por fim concluímos que, a deficiência do estrogênio influencia na progressão da periodontite apical, potencializando a mesma. E isso ocorre principalmente em função da hipoestrogenia agravar a perda óssea alveolar por meio da regulação osteoclástica durante a periodontite apical.

Desta forma, nosso estudo reforça que medidas preventivas como a suplementação estrogênica pode levar ao controle da perda óssea, da progressão da periodontite apical e à resistência à disseminação de infecções dentoalveolares.

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Anexo 1- Registro do protocolo de revisão sistemática na base PROSPERO

Número de registro: CRD42021269555

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Bárbara Romagna Rossetti, Angélica Fensterseifer Lemos, Marcus Vinícius Reis Só. What is the influence of estrogen deficiency on progression of apical periodontitis? Systematic review of preclinical studies.. PROSPERO 2021 CRD42021269555 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021269555

Review question [1 change]

Does estrogen deficiency interfere with the progression of apical periodontitis in rat model?

Context and rationale

Under normal conditions, bone metabolism is characterized by a balance between bone formation and resorption. However, in estrogen deficiency, there is an imbalance in bone remodeling, which results in a reduction in bone mass, characterizing osteoporosis. As there is little evidence in human studies about the association of estrogen deficiency and the progression of apical periodontitis, however, there are several studies in animal models, which indicate that an osteoporotic condition delays or hinders the repair of periapical lesions. This review will study the influence of estrogen deficiency on the repair process of periapical lesions induced in animal models, specifically in rats.

Searches

MEDLINE/PubMed, EMBASE, Cochrane Library, OpenGrey, Web of Science and Scopus electronic databases will be searched to identify relevant articles. No publication date or language restrictions will be applied. Additionally, to locate any potential unidentified study, the search strategy will also include a manual search of bibliographies and

reference lists of the included studies. The search strategy will include terms relating to the PICOs principles

of the present systematic review. The search will be carried out one more time before the final analysis in order to include the most recent studies.

Study designs to be included [1 change]

Inclusion criteria:

Experimental studies with laboratory animals.

Exclusion criteria:

1. Observational studies

a. Descriptive: Case report and series; cross sectional surveys

b. Analytic: Ecological, cross-sectional, case-control and cohort studies.

2. Experimental studies:

a. Clinical trials

b. Field trials

c. Community trials

Human disease modelled

Estrogen deficiency

Animals/population [1 change]

Inclusion criteria:

All animal models (female, all species) with estrogen deficiency, teeth with apical periodontitis and periapical lesion formation. Evaluation of the progression of apical periodontitis and bone repair

Exclusion criteria:

1. Animals with other systemic diseases

2. Animal models that do not present a hypoestrogenic group (control group)

3. Ex vivo models;

Intervention(s), exposure(s) [1 change]

Inclusion criteria:

Apical periodontitis can be induced through pulp exposure to the oral environment, with or without the insertion of pathogens and/or inflammatory cytokines. Osteoporotic-like bony phenotype may be induced in animals by ovariectomy or orchiectomy procedures.

Exclusion criteria:

Presence of other comorbities.

Comparator(s)/control [1 change]

Inclusion criteria:

Control groups are those with no estrogen deficiency induction (SHAM groups/control groups) or hormonal control through drug therapy.

Exclusion criteria:

Studies that do not have a control group for comparison.

Other selection criteria or limitations applied

Outcome measure(s) [1 change]

Inclusion criteria:

Progression of apical periodontitis in hypoestrogenic animals (e.g., by imaging,

histomorphometric and/or immunohistochemical methods).

Exclusion criteria:

No assessment of the progression of apical periodontitis after induction of estrogen deficiency;

Study selection and data extraction [1 change]

Procedure for study selection

Titles and abstracts of all studies retrieved from the search strategy will be reviewed and, based on the inclusion/exclusion criteria, full texts will be selected for complete review. All papers will be reviewed independently by two reviewers, and, in case of disagreements a third reviewer will be discussing for

concordance.

Prioritise the exclusion criteria

Exclusion criteria:

1. Animals with other systemic diseases;

2. Animal models that do not present a hypoestrogenic group (control group);

3. Ex vivo models;

4. Other studies designs

5. No assessment of the progression of apical periodontitis after induction of estrogen deficiency;

Methods for data extraction

Two reviewers will extract the following information from the selected studies: (1) publication details (first author and year); (2) sample species and sample size; (3) sample characteristics (n per groups); (4) hormone deficiency induction methods; (5) hormonal control method; (6) apical periodontitis induction method; (7) teeth evaluated; (8) evaluation of apical periodontitis; (9) period evaluated; (10) outcomes; and (6) main findings. Data will be extracted from the text, and in case of lack of data the authors will not be contacted. In case of disagreement between reviewers, a third reviewer will be consulted and will be responsible for the decision.

Data to be extracted: study design

a. Number of groups

b. Number of animals in experimental and control groups

Data to be extracted: animal model

The following items will be extracted from the animal models:

(a) Animal species

(b) Strain

(c) Age

(d) Weight

(e) Gender

(f) Experimental groups characteristics

(g) Control group characteristics (SHAM surgery, e.g.)

Data to be extracted: intervention of interest

a) apical periodontitis induction method (e.g pulp exposure; pulpectomy)

b) hormonal control method

c) hormonal deficiency induction method

d) bite

e) evaluation of apical periodontitis

f) experimental period

Data to be extracted: primary outcome(s)

1. Proportion of lost bone volume / total volume of periapical lesion - unit: percentage (%) - continuous quantitative variable - 0 to 100.

2. Total area of ??lost bone - unit: mm2 - continuous variable

3. Total volume of lost bone - unit: mm3 - continuous variable

Data to be extracted: secondary outcome(s)

None.

Data to be extracted: other

None.

Risk of bias and/or quality assessment

By use of SYRCLE's risk of bias tool.
The Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE) risk of bias tool will be used to assess the quality of available evidence. The items here will be scored as Yes, No, or Unclear. Two reviewers will conduct the process of evaluating the risk of bias of the included studies; in case of disagreement, the study will be discussed with a third one..

Strategy for data synthesis [1 change]

Planned approach

The included studies will be analyzed quantitatively. A narrative synthesis of the findings will be provided regarding the different results in alveolar bone density of periapical lesions. Quantitative analysis will be performed after assessing the heterogeneity among eligible studies. Eligible studies will be those with quantitative findings, such as the mean proportion between lost bone and total volume; average total area of ??lost bone; and mean number of lost bone trabeculae. Heterogeneity will be formally assessed using the Q-statistic test based on 2 and the I^2 statistic (I^2). I^2>50% or p<0.1 will be considered indicators of substantial heterogeneity. If the heterogeneity test reveals that the eligible studies are the same, a meta-analysis will be performed.

Effect measure

Outcome measure 1 - ratio of lost bone volume / total periapical lesion volume (%) - mean difference.

Outcome measure 2 - total area of ??lost bone - mean difference.

Outcome measure 3 - number of lost bone trabeculae - mean difference.

Effect models

Random-effects model will be used for all outcome measures since a great diversity of protocols is usually observed in animal studies.

Heterogeneity

The heterogeneity will be assessed through The Review Manager software (RevMan Version 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) which will be employed to perform the whole meta-analysis. The heterogeneity between eligible studies will be evaluated using the Q^2 -based Q-statistic test and the I^2 (I^2) statistic. I^2>50% or $p < 0.1$ will be considered indicators of substantial heterogeneity.

Other

None.

Analysis of subgroups or subsets [1 change]

Subgroup analyses

The subgroups or subsets will be defined according to the data provided by the included studies.

Sensitivity

None planned.

Publication bias

None planned.

Contact details for further information

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Organisational affiliation of the review

Federal University of Rio Grande do Sul

Review team members and their organisational affiliations

Mrs Bárbara Romagna Rossetti. Universidade Federal do Rio Grande do Sul
Mrs Angélica Fensterseifer Lemos. Universidade Federal do Rio Grande do Sul
Dr Marcus Vinícius Reis Só. Universidade Federal do Rio Grande do Sul

Review type

Experimental animal exposure review

Anticipated or actual start date

02 August 2021

Anticipated completion date

01 March 2022

Funding sources/sponsors

None.

Conflicts of interest

Language

English

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Animals; Disease Progression; Endocrine System Diseases; Estrogens; Periapical Periodontitis; Research

Date of registration in PROSPERO

30 September 2021

Date of first submission

03 August 2021

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

30 September 2021

Anexo 2 – Normas da Revista International Journal Endodontic

Folha de rosto

A folha de rosto deve conter:

- Título
- Inicial(is) e sobrenome de cada autor
- Nome e endereço do departamento
- Título corrido
- Não mais de seis palavras-chave (em ordem alfabética)
- Nome, endereço postal completo, telefone, fax e e-mail do autor responsável pela correspondência.

Resumo

Não deve ter mais de 350 palavras usando a seguinte estrutura, quando aplicável:

- Título
- Antecedentes
- Objetivos
- Métodos
- Resultados
- Discussão
- Conclusões
- Financiamento
- Registro

Texto Principal

Deve ser dividido em Introdução, Métodos, Resultados, Discussão, Conclusões, Financiamento e Conflito de Interesses

- Introdução: Deve ser focado para contextualizar o assunto e justificar a necessidade da revisão.
- Método: Dividir em subseções lógicas para melhorar a legibilidade e melhorar a

compreensão

- Resultados: Apresentar de forma estruturada
- Discussão: Deve resumir os resultados, destacando completude e aplicabilidade das evidências
- Conclusão: A seção deve chegar a conclusões e/ou recomendações claras com base nas evidências apresentadas.
- Financiamento: Forneça a fonte primária de financiamento
- Conflito de interesse: Necessidade de especificar potenciais conflitos de interesse para todos os autores. Se não houver conflito, os autores devem declará-lo explicitamente.

Referências

No texto:

- Autores simples ou duplos devem ser citados juntamente com o ano de publicação, ex. (Pitt Ford & Roberts 1990).
- Se houver mais de dois autores, o primeiro autor seguido de et al. é suficiente, e. (Tobias et al. 1991).
- Se mais de 1 artigo for citado, as referências devem estar em ordem de ano e separadas por "," ex. (Pitt Ford & Roberts 1990, Tobias et al. 1991).

Lista de referências: Todas as referências devem ser reunidas no final do trabalho em ordem alfabética e devem estar no seguinte formato:

- Nomes e iniciais de até seis autores. Quando houver sete ou mais, liste os três primeiros e adicione et al.
- Ano de publicação entre parênteses
- Título completo do trabalho seguido de ponto final (.)
- Título do periódico completo (em itálico)
- Número do volume (negrito) seguido por uma vírgula (,)
- Primeira e última páginas

Seguem exemplos de formas corretas de referência:

Artigo de jornal padrão

Bergenholtz G, Nagaoka S, Jontell M (1991) Classe II que expressam células em pulpite induzida experimentalmente. International Endodontic Journal 24, 8-14.

Autor corporativo

British Endodontic Society (1983) Diretrizes para tratamento de canal radicular. International Endodontic Journal 16, 192-5.

Suplemento do diário

Frumin AM, Nussbaum J, Esposito M (1979) Asplenia funcional: demonstração da atividade esplênica por varredura da medula óssea (Resumo). Sangue 54 (Supl. 1), 26a.

Livros e outras monografias

Autor(es) pessoal(is)

Gutmann J, Harrison JW (1991) Surgical Endodontics, 1st edn Boston, MA, EUA: Blackwell Scientific Publications.

Capítulo em um livro

Wesselink P (1990) Terapia convencional de canal III: obturação radicular. In: Harty FJ, ed. Endodontia na Prática Clínica, 3ª ed.; págs. 186-223. Londres, Reino Unido: Butterworth.

Documento de atas publicado

DuPont B (1974) Transplante de medula óssea em imunodeficiência combinada grave com um doador compatível com MLC não relacionado. In: White HJ, Smith R, eds. Anais da Terceira Reunião Anual da Sociedade Internacional de Rematologia Experimental; págs. 44-46. Houston, TX, EUA: Sociedade Internacional de Hematologia Experimental.

Publicação da agência

Ranofsky AL (1978) Operações Cirúrgicas em Hospitais de Curta Duração: Estados Unidos-1975. Publicação DHEW nº. (PHS) 78-1785 (Estatísticas Vitais e de Saúde; Série 13; nº 34.) Hyattsville, MD, EUA: Centro Nacional de Estatísticas de Saúde.8

Dissertação ou tese

Saunders EM (1988) Investigações in vitro e in vivo sobre obturação do canal radicular usando técnicas de guta-percha amolecidas termicamente (Tese de Doutorado). Dundee, Reino Unido: Universidade de Dundee.

Tabelas, Figuras e Legendas de Figuras

Tabelas:

- As tabelas devem estar em espaço duplo
- Sem linhas verticais, com uma única linha em negrito abaixo dos títulos das colunas.
- As unidades de medidas devem ser incluídas no título da coluna.

Figuras:

- Todas as figuras devem ser planejadas para caber na largura de 1 coluna (8,0 cm), largura de 1,5 coluna (13,0 cm) ou largura de 2 colunas (17,0 cm), e devem ser adequadas para reprodução por fotocópia da versão impressa do manuscrito.
- As letras nas figuras devem ser em um tipo de letra sem serifa (por exemplo, Helvetica); se possível, o mesmo tipo de letra deve ser usado para todas as figuras em um papel.
- Após a redução para publicação, o texto e os números em caixa alta devem ter pelo menos 1,5-2,0 mm de altura (10 pontos Helvetica).
- Após a redução, os símbolos devem ter pelo menos 2,0-3,0 mm de altura (10 pontos).
- Todas as fotografias em meio-tom devem ser enviadas em tamanho de reprodução final. Em geral, as figuras de várias partes devem ser organizadas como apareceriam na versão final.
- A redução à escala que será usada na página não é necessária, mas quaisquer requisitos especiais (como a distância de separação de pares estéreo) devem ser claramente especificados.

Legendas das figuras:

- As legendas das figuras devem começar com um breve título para toda a figura e continuar com uma breve descrição de cada painel e os símbolos utilizados; eles não devem conter nenhum detalhe de métodos.

Anexo 3- Aprovação da COMPESQ-ODO-UFRGS

UFRGS

Linhas de Pesquisa
Projetos de Pesquisa
Áreas de Atuação
Bolsas de Pesquisa
Iniciação Científica/Tecnológica Voluntário
Programa de Fomento à Pesquisa(auxílio)

Projeto N°: 41151 **Título:** QUAL A INFLUENCIA DA DEFICIENCIA DE ESTROGENIO NA PROGRESSAO DA PERIODONTITE APICAL? REVISAO SISTEMATICA DE ESTUDOS PRE CLINICOS

Área de conhecimento: Endodontia **Início:** 01/09/2021 **Previsão de conclusão:** 01/03/2022

Situação: Projeto em Andamento

Origem: Faculdade de Odontologia
Programa de Pós-Graduação em Odontologia

Projeto da linha de pesquisa: EPIDEMIOLOGIA, ETIOPATOGENIA E REPERCUSSÃO DAS DOENÇAS DA CAVIDADE BUCAL E ESTRUTURAS ANEXAS

Local de Realização: não informado

Não apresenta relação com Patrimônio Genético ou Conhecimento Tradicional Associado.

Objetivo:

O objetivo desse estudo consiste em avaliar a existência de evidências científicas a fim de verificar a influência da deficiência de estrogênio no processo de reparo de lesões periapicais induzidas. Uma busca sistemática, seguindo as diretrizes PRISMA, baseada no protocolo PICOS, será realizada utilizando termos MeSH e termos comuns ao assunto utilizando as plataformas PubMed, Cochrane, Scopus, Web of Science e Open Grey. Os critérios de elegibilidade, com base na estratégia PICOS, serão: animais com

Palavras Chave:

ENDODONTIA

Equipe UFRGS:

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Avaliações:

Comissão de Pesquisa de Odontologia - **Aprovado** em 16/08/2021 Clique aqui para visualizar o parecer

Anexo 4 – Estratégia de busca para cada base de dados

Database	Search strategy	Findings
MEDLINE/PubMed	#1: (((((((metabolic diseases) OR (diseases, metabolic)) OR (bone diseases)) OR (bone diseases, metabolic)) OR (osteoporosis)) OR (ovariectomy)) OR (estrogen-deficient state)) OR (estrogen deficiency)) OR (estrogen)	2.020.986
	#2: (((((periapical lesion) OR (periapical periodontitis)) OR (periodontitis, apical)) OR (periapical diseases)) OR (apical peridontitis)) OR (periodontitis, periapical)	11.443
	#3: (((model, animal) OR (animal model)) OR (rat)) OR (rat model)	2.457.878
	#1 AND #2 AND #3	214
Cochrane Library	#1: metabolic diseases OR diseases, metabolic OR bone diseases OR bone diseases, metabolic OR osteoporosis OR ovariectomy OR estrogen-deficient state OR estrogen deficiency OR estrogen	40.390
	#2: periapical lesion OR periapical periodontitis OR periodontitis, apical OR periapical diseases OR apical peridontitis OR periodontitis, periapical	1191
	#3: model, animal OR animal model OR rat OR rat model	14934
	#1 AND #2 AND #3	16
Scopus	#1: (TITLE-ABS-KEY (metabolic AND diseases) OR TITLE-ABS-KEY (diseases, AND metabolic) OR TITLE-ABS-KEY (bone AND diseases) OR TITLE-ABS-KEY (bone AND diseases, AND metabolic) OR TITLE-ABS-KEY (osteoporosis) OR TITLE-ABS-KEY (ovariectomy) OR TITLE-ABS-KEY (	1.226.751

	estrogen-deficient AND state) OR TITLE-ABS-KEY (estrogen AND deficiency) OR TITLE-ABS-KEY (estrogen))	
	#2: (TITLE-ABS-KEY (periapical AND lesion) OR TITLE-ABS-KEY (periapical AND periodontitis) OR TITLE-ABS-KEY (periodontitis, AND apical) OR TITLE-ABS-KEY (periapical AND diseases) OR TITLE-ABS-KEY (apical AND peridontitis) OR TITLE-ABS-KEY (periodontitis, AND periapical))	12.637
	#3: (TITLE-ABS-KEY (model, AND animal) OR TITLE-ABS-KEY (animal AND model) OR TITLE-ABS-KEY (rat) OR TITLE-ABS-KEY (rat AND model))	3.794.016
	#1 AND #2 AND #3	338
Web of Science	#1: TS=(metabolic diseases OR diseases, metabolic OR bone diseases OR bone diseases, metabolic OR osteoporosis OR ovariectomy OR estrogen-deficient state OR estrogen deficiency OR estrogen)	670.781
	#2: TS=(periapical lesion OR periapical periodontitis OR periodontitis, apical OR periapical diseases OR apical peridontitis OR periodontitis, periapical)	6.496
	#3: TS=(model, animal OR animal model OR rat OR rat model)	2.256.615
	#1 AND #2 AND #3	139
EMBASE	#1: metabolic AND diseases OR (diseases, AND metabolic) OR (metabolic AND bone AND disease) OR (bone AND diseases, AND metabolic) OR osteoporosis OR ovariectomy OR ('estrogen deficient' AND state) OR (estrogen AND deficiency) OR estrogen	659.639

	#2: periapical AND lesion OR (periapical AND periodontitis) OR (periodontitis, AND apical) OR (periapical AND diseases) OR (apical AND peridontitis) OR (periodontitis, AND periapical)	5.980
	#3: model, AND animal OR (animal AND model) OR rat OR (rat AND model)	3.560.098
	#1 AND #2 AND #3:	31
Grey Literature Report	#1: metabolic diseases OR diseases, metabolic OR bone diseases OR bone diseases, metabolic OR osteoporosis OR ovariectomy OR estrogen-deficient state OR estrogen deficiency OR estrogen	0
	#2: periapical lesion OR periapical periodontitis OR periodontitis, apical OR periapical diseases OR apical peridontitis OR periodontitis, periapical	0
	#3: model, animal OR animal model OR rat OR rat model	0
	#1 AND #2 AND #3	0