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Major clinical outcomes of the endodontic infections and gut microbiota axis: a systematic review

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Abstract

Introduction: Endodontic therapy aims to shape, clean, and disinfect the root canal, and is performed by removing all pulp tissue or necrotic remains and microorganisms present in the root canal system. The gut microbiota or specific microbial metabolites not only locally influence the host's inflammatory responses, nutritional intake, or intestinal barrier function, but are also related to the immune and metabolic systems. In addition to antimicrobial activity, calcium hydroxide has properties such as dissolution of organic remnants, anti-inflammatory action, inhibition of inflammatory resorptions, and physical barrier function. **Objective:** To present the main considerations and clinical outcomes of the relationship between gut microbiota and endodontic infections and highlight endodontic treatment with calcium hydroxide, showing the mechanisms of antibacterial action. **Methods:** The PRISMA Platform systematic review rules were followed. The search was conducted from September to October 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 102 articles were found, 25 were evaluated in full and 09 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 35 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2. Most studies did not show homogeneity in their results, with X^2=79.2%<50%. It was concluded that, in the setting of endodontic therapy, the presence of microorganisms, particularly gramnegative anaerobes, in the root canal system and cementum resorption gaps after root canal treatment is considered one of the main causes of persistent periapical lesions and, therefore, of endodontic treatment failure. The gut microbiota or specific microbial metabolites not only locally influence the patient's inflammatory responses, nutritional intake, or intestinal barrier function, but are also related to the immune and metabolic systems. The change in the microbiota of the oral-gut axis and its interactions with Helicobacter pylori may be potential targets for the diagnosis and infectious treatment of Helicobacter pylori. Calcium hydroxide in endodontics is the most widely used medication to combat pathology-causing bacteria, but when used alone it may not be able to eliminate these microorganisms. The combination of other medications incorporated into calcium hydroxide contributes to positive results with the elimination of more resistant bacteria.

Keywords: Endodontics. Endodontic treatment. Gut microbiota. Oral microbiota. Calcium hydroxide.

Introduction

Endodontic therapy aims to shape, clean, and disinfect the root canal and is performed by removing all pulp tissue or necrotic remains and microorganisms present in the root canal system. This procedure is followed by root canal obturation to fill all space, preventing new bacterial invasion and colonization, in addition to preventing remaining bacteria from reaching the periapical tissues [1,2].

In this context, the gut microbiota stands out, with trillions of intestinal microorganisms that interact with the host through the release of various signals and affect the development, physiology, and general health of the patient. The gut microbiota or specific microbial metabolites not only locally influence the host's inflammatory responses, nutritional intake, or intestinal barrier function, but are also related to the immune and metabolic systems [3].

Accumulating evidence has revealed the essential effects of the gut microbiota on bone health through the gut-alveolar-bone axis. Intestinal pathogens or metabolites can translocate to the distant alveolar bone via circulation and regulate bone homeostasis. In addition, intestinal pathogens can induce aberrant intestinal immune responses and subsequent homing of immunocytes to distant organs, contributing to pathological bone loss [4].

In this sense, a large number of studies have been focused on the development of basic and clinical concepts that guide the endodontic treatment of teeth without pulp vitality and their relationship with the gut microbiota [5,6]. Pulp necrosis represents the death of the pulp, meaning the cessation of its metabolic processes, with consequent loss of its structure as well as its natural defenses. The necrotic pulp tissue, decomposing and disintegrating, will allow the invasion of bacteria, which will find ideal conditions for multiplication, propagation, and proliferation. Concomitantly with the necrosis process, contamination of the root canal occurs, which is of fundamental importance for the establishment of periapical pathology [6-10].

In long-term infectious processes, mainly due to the nutritional relationships between microorganisms, combined with the gradual drop in oxygen tension inside the root canals, there is a process of natural selection (microbial shift) leading to a predominance of gram-negative microorganisms, not only in the root canal lumen but also throughout the root canal system [1-3].

In addition to having different virulence factors that generate toxic products and byproducts to periapical tissues, gram-negative microorganisms contain an endotoxin (lipopolysaccharide - LPS) in their cell wall, which is released during bacterial multiplication or death, responsible for a series of biological effects, promoting an inflammatory reaction and bone resorption in the periapical region [4,5].

The majority of endodontic infections are mixed and polymicrobial, with a predominance of strict anaerobes. However, the presence of Enterococcus faecalis, a facultative anaerobic bacterium that is highly resistant to endodontic treatment, has been observed. This microorganism has been frequently found in root canals infected for a long time and with large periapical lesions, causing infections that are difficult to treat [1].

Given this, it is observed that the control of endodontic infection requires a balance of the gut microbiota, as well as a correct chemical-mechanical preparation, responsible for the chemical and mechanical removal of microorganisms, through the auxiliary chemical substance and the action of the instruments and, if necessary, the use of an intracanal medication. In addition to these factors, hermetic obturation, with maximum waterproofing and minimum aggression to living tissues, is an essential factor for the success of endodontic treatment [2-4].

Among the substances proposed as a delayed dressing in the endodontic treatment of teeth with chronic periapical reaction, calcium hydroxide stands out, which has been widely disseminated, particularly due to its antimicrobial properties. In addition to antimicrobial activity, calcium hydroxide has properties such as dissolution of organic remains, anti-inflammatory action, inhibition of inflammatory reabsorptions, and the function of a physical barrier [11-14].

Thus, the present study aimed to present the main considerations and clinical outcomes of the relationship between gut microbiota and endodontic infections, as well as highlight endodontic treatment with calcium hydroxide, showing the mechanisms of antibacterial action.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/10/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 09/10/2024.

Data Sources and Research Strategy

The literary search process was carried out from September to October 2024 and was developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (DeCS/MeSH Terms) were used: *"Endodontics. Endodontic treatment. Gut* *microbiota. Oral microbiota. Calcium hydroxide"*, and using the Boolean "and" between the *MeSH* terms and "or" between historical discoveries.

Study Quality and Risk of Bias

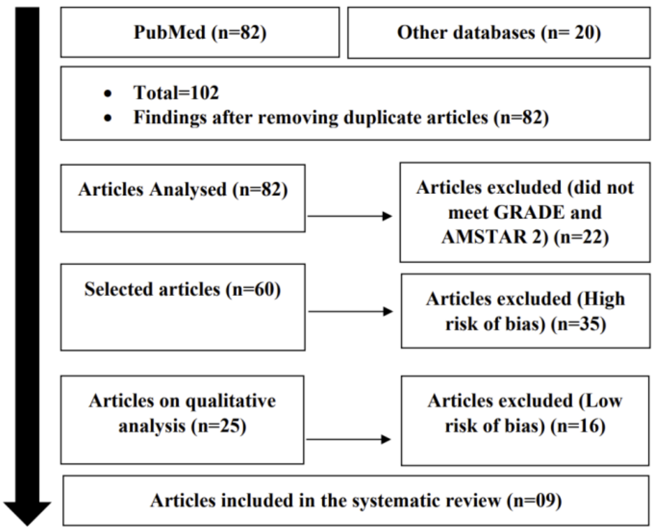
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 102 articles were found that were subjected to eligibility analysis, with 09 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=79.2%<50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 35 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

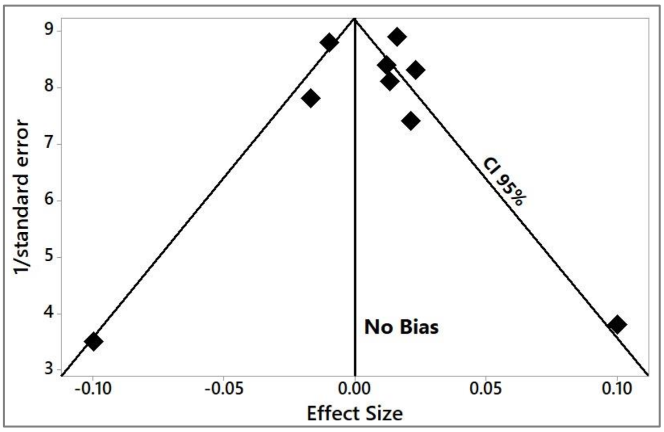
Figure 1. Articles eligibility process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=09 studies).



Source: Own authorship.

Major Outcomes

The ideal endodontic treatment aims to clean and shape the entire root canal system, seeking to eliminate the infection, aided by indicated irrigating solutions and appropriate intracanal medications, so that, in the end, a satisfactory obturation of the root canal system is obtained [1-3].

The periapical lesion represents the localized immuno-inflammatory response due to the increase in the number and progression of microorganisms from the contaminated root canals toward the apical and periapical tissues resulting in bone and tooth resorption. The periapical inflammatory reaction is composed of a mixed inflammatory infiltrate, characterized by the presence of neutrophils, T and B lymphocytes, plasma cells, and macrophages, with a greater cellular prevalence depending on the stage of the disease [1-4].

In the human body, the oral cavity and the intestine are the most complex and interdependent microbial habitats. *Helicobacter pylori* is one of the most important pathogens of the digestive tract, especially the stomach, due to its direct relationship with many gastric diseases, including gastric cancer. *Helicobacter pylori* infections can destroy the normal gastric environment and make the stomach a habitable conduit to improve microbial interactions between the oral cavity and the intestine, thus remodeling the oral and intestinal microbiomes. *Helicobacter pylori* can also be detected in the mouth and intestine, while the interaction between the microbiota of the oral-gut axis. The change of the microbiota of the oral-gut axis and its interactions with *Helicobacter pylori* may be potential targets for the diagnosis and treatment of *Helicobacter pylori* infections [15].

The presence of microorganisms, particularly gram-negative anaerobes, in the root canal system and cementum resorption gaps after root canal treatment is considered one of the main causes of persistent periapical lesions and, therefore, endodontic treatment failure. Furthermore, in experimental models of periodontal disease and periapical lesions, the presence of bacteria stimulates the local inflammatory response and the intense production of proteases that degrade the extracellular environment and facilitate the bone resorption process. Currently, calcium hydroxide has been considered the intracanal medication of choice because it presents properties such as microbial control, dissolution of organic debris, anti-inflammatory power, and inhibition of inflammatory resorptions [10].

Calcium hydroxide ($Ca\ (OH)_2$) was introduced into endodontics by Hermann in 1920 in the form of Calxyl paste, and since then it has been considered the drug of choice for the treatment of root canals with pulp necrosis, due to its excellent antimicrobial and biological properties. In addition, this drug is characterized by being a strong base, with a pH of approximately 12.5. It is presented in the form of a white, odorless powder, and therefore needs to be added to a vehicle for clinical use. Calcium hydroxide paste dissociates into calcium and hydroxyl ions, which are responsible for conferring excellent properties to the drug [10,11].

Also, calcium hydroxide has two expressive enzymatic properties: inhibiting bacterial enzymes, generating an antimicrobial effect, and activating tissue enzymes, such as alkaline phosphatase, influencing tissue mineralization. Alkaline phosphatase is a hydrolytic enzyme that acts by releasing inorganic phosphate from phosphate esters. Calcium hydroxide activates alkaline phosphatase at high pH, which can initiate or promote mineralization [11,12].

Furthermore, most microorganisms related to endodontic infection do not survive at alkaline pH, and the main antimicrobial action of calcium hydroxide is related to the alkalinization of the dentin mass. Hydroxyl ions are highly oxidizing free radicals that are extremely reactive, reacting with many biomolecules. This reactivity is high and indiscriminate, so these free radicals rarely diffuse far from the sites of generation. The lethal effect of hydroxyl ions on bacterial cells probably occurs through the mechanisms presented in Table 1 [13,14].

Table 1. Mechanisms of the lethal effect of hydroxyl ions on bacterial cells.

❖ *Damage to the bacterial cytoplasmic membrane. Hydroxyl ions induce lipid peroxidation destroying membrane phospholipids, removing hydrogen atoms from unsaturated fatty acids, generating lipid free radicals that react with oxygen, forming a lipid peroxide radical, which removes another hydrogen atom from the second fatty acid, generating another lipid peroxide, which, in turn, act as free radicals, initiating an autocatalytic reaction, which causes extreme destruction of the bacterial membrane;*
❖ *Protein denaturation. With the increase in pH promoted by calcium hydroxide, there is an induction of ionic adhesion breakdown that maintains the tertiary structure of the protein, as a consequence the enzyme remains with its covalent structure. With the loss of the biological activity of the enzyme and interruption of cellular metabolism, structural proteins can also be damaged by hydroxyl ions;*
❖ *Damage to bacterial DNA. Hydroxyl ions react with bacterial DNA and induce doublestrand breakage, genes are lost, and as a result, replication and cellular activity are inhibited and cellular activity becomes disorganized. Free radicals can also induce lethal mutations in cells.*

Source: [13,14].

Moreover, calcium hydroxide has been widely used in endodontics, specifically in pulp protection and pulpotomies, as a temporary dressing between sessions and in the composition of filling cement. The effects of calcium hydroxide are attributed to its dissociation into hydroxyl ions (OH^-) and calcium ions (Ca^+). In the extracellular environment, calcium hydroxide has mineralizing properties, since hydroxyl ions are involved in maintaining an alkaline environment and calcium ions affect the mineralization of the extracellular matrix [11-13].

Previous studies have shown that the application of calcium hydroxide inside root canals allows the deposition of a mineralized tissue similar to cementum by periodontal ligament cells, obliterating the foraminal opening. It was demonstrated that the use of calcium hydroxide as a delay dressing in teeth with periapical lesions allowed biological sealing of the apical foramen, unlike teeth with periapical lesions submitted to endodontic treatment in a single session, in which the deposition of cemented tissue was not observed [11-14].

The deposition of mineralized tissue in the specimens of this group was more advanced than in those teeth with pulp vitality submitted to endodontic treatment, suggesting a role for calcium hydroxide in apical cementogenesis. As a result of this observation, the present study was proposed to evaluate the effects of the increase in the extracellular concentration of calcium on the differentiation of periodontal ligament cells into cementoplasts and subsequent cementogenesis. More specifically, the neoformation of cementum was evaluated *in vivo* in an animal model, and from the results obtained, they were involved in the proliferation, migration, differentiation, and mineralization mediated by human periodontal ligament cells [12].

Another important property of calcium hydroxide is its antimicrobial effect, due to its dissociation into hydroxyl ions that allow the medium to become alkaline, altering the action of the enzymes present in the bacterial cell wall, which is essential for cellular metabolism [13,14]. It is also noted that, because it is in powder form, calcium hydroxide must be associated with other substances to be inserted into the root canal.

The calcium hydroxide used in endodontic practice is manipulated with saline solution, which is water-soluble and, as these are an association, together they have chemical characteristics of dissociation, diffusibility, and filling capacity that are decisive for biological behavior. However, specific microorganisms, mainly Enterococcus faecalis, are resistant to $Ca(OH)_2$. Thus, research has been developed adding vehicles with antimicrobial properties associated with calcium hydroxide to increase this activity, without losing its other characteristics [13].

The stages of endodontic treatment are interdependent and it is necessary to pay close attention to each stage to ensure the success of the treatment. Therefore, the removal of calcium hydroxide-based pastes from the interior is also of great importance. Before filling the canal system, all $Ca(OH)_2$ must be removed. The remains of this medication present inside the root canals can form a type of barrier, thus hindering the leakage of the cement across the entire dentin surface, preventing the formation of an efficient seal for the success of the endodontic treatment [12-14].

Conclusion

It was concluded that, in the context of endodontic therapy, the presence of microorganisms, particularly gram-negative anaerobes, in the root canal system and cementum resorption gaps after root canal treatment is considered one of the main causes of persistent periapical lesions and, therefore, of endodontic treatment failure. The gut microbiota or specific microbial metabolites not only locally influence the patient's inflammatory responses, nutritional intake, or intestinal barrier function, but are also related to the immune and metabolic systems. The change in the microbiota of the oralintestinal axis and its interactions with *Helicobacter pylori* may be potential targets for the diagnosis and infectious treatment of *Helicobacter pylori*. Calcium hydroxide in endodontics is the most widely used medication to combat bacteria that cause pathology, but when used alone it may not be able to eliminate these microorganisms. The combination of other medications incorporated into calcium hydroxide contributes to positive results with the elimination of more resistant bacteria.

CRediT

Author contributions: **Conceptualization -** Fawana Estolomo de Freitas Neves, Yuri Furtado Pagioro; **Data curation-** Fawana Estolomo de Freitas Neves, Yuri Furtado Pagioro; **Formal Analysis-** Fawana Estolomo de Freitas Neves, Yuri Furtado Pagioro, Fábio Pereira Linhares de Castro; **Investigation-** Fawana Estolomo de Freitas Neves, Yuri Furtado Pagioro; **Methodology-** Fawana Estolomo de Freitas Neves, Yuri Furtado Pagioro, Fábio Pereira Linhares de Castro; **Project administration-** Fawana Estolomo de Freitas Neves, Yuri Furtado Pagioro, Fábio Pereira Linhares de Castro; **Supervision**Fábio Pereira Linhares de Castro; **Writing - original draft-** Fawana Estolomo de Freitas Neves, Yuri Furtado Pagioro, Fábio Pereira Linhares de Castro; **Writing-review & editing-** Fawana Estolomo de Freitas Neves, Yuri Furtado Pagioro, Fábio Pereira Linhares de Castro.

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

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