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Mechanism Underlying the Alveolar Bone Destruction by *Prevotella intermedia*: Systematic Review

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Abstract

Introduction: Periodontitis is an inflammatory disorder caused by oral microorganisms, including *Prevotella intermedia*, that destroy the periodontal ligament and alveolar bone. The detailed mechanism of *P. intermedia*-inducing bone damage is essential to establish a novel approach to controlling *P. intermedia* that prevents alveolar bone loss. **Purpose:** To elucidate the mechanism of *P. intermedia*'s role in alveolar bone destruction by systematically reviewing various related publications. **Methods:** From September 2020 through February 2021, this systematic review was performed by selecting publications for relevant material from two electronic databases, PubMed and Scopus. The literature must be in English, published within the last ten years, be available in full-text form, and be a research article to meet the criteria for inclusion. **Results:** Three final articles passed the eligibility evaluation stage and met the inclusion requirements. They all discussed how *P. intermedia* lipopolysaccharide (LPS) affects target cells to destroy bone, including human dental follicle stem cells (hDFSCs), human periodontal ligament fibroblasts (hPDLs), and macrophages. Tumor necrosis factor (TNF), interleukin-6 (IL-6), IL-8, and prostaglandin E2 (PGE2) are a few of the inflammatory mediators that LPS *P. intermedia* cause a rise in target cells, leading to bone damage. These inflammatory mediators stimulate nuclear factor-kappa ligand receptor (RANKL) expression, resulting in osteoclast activation and differentiation, leading to bone loss. **Conclusion:** *P. intermedia* significantly contributes to alveolar bone degradation by enhancing inflammatory mediators. As observed in periodontitis, these mediators stimulate RANKL expression and osteoclast activation, resulting in alveolar bone damage.

Keywords: Bone destruction; Inflammatory response; *Prevotella intermedia*; Periodontitis

Introduction

Periodontitis is a chronic inflammatory disease induced by biofilms that cause loss of connective tissue and supporting alveolar bone, resulting in tooth loss.[1-3] This disease results from an infection that previously existed in the gums or is called gingivitis. Gram-negative bacteria colonizing the gingival sulcus cause inflammation and immune response with protective and destructive roles.[4-6] Chronic periodontitis usually has no symptoms until the disease becomes severe and causes the teeth to move until they fall out. In addition,

periodontitis also has a role in initiating or developing other systemic diseases such as heart disease, stroke, and diabetes.[1]

The primary etiology of periodontitis is plaque accumulation caused by oral bacteria. The bacterial species associated with periodontitis include *Porphyromonas gingivalis*, *Treponema denticola*, *Prevotella intermedia,* and *Aggregatibacter actinomycetemcomitans*.[7] These bacteria then interact with the host's immune system, causing inflammation and disease.[8,9] Several other factors can increase the risk of periodontitis, such as smoking and alcohol consumption, HIV and AIDS, stress, diabetes, and osteoporosis.[1,7]

The bacteria that cause periodontitis adapt well to their environment by producing virulence factors to ensure their survival in the oral cavity.[10] For example, *P. intermedia* has a virulence factor in the form of lipopolysaccharide (LPS), a component of this bacterium's outer membrane. LPS can trigger host cells to release inflammatory mediators stimulating osteoclast differentiation and activation.[11] In addition, a leucine-rich repeat (LRR) domain protein has been shown to enable pathogens to attach and be internalized by host cells. The ability of bacteria to be internalized allows them to escape the control of the immune system so that the bacteria can survive.[12]

One of the characteristics of periodontitis is alveolar bone resorption induced by osteoclasts.[13] Bone is a very dynamic and active tissue. Bone undergoes constant renewal in response to mechanical, nutritional, and hormonal influences. A balance between bone resorption by osteoclasts, bone formation by osteoblasts, and osteocytes to sense the mechanical load is necessary in healthy adults.[14–16] Thus, bone resorption by osteoclasts and bone formation by osteoblasts play major roles in calcium homeostasis, which is required for bone growth, remodeling, and maintenance. An imbalance in bone resorption by osteoclasts and bone formation by osteoblasts can cause bone destruction.[14,17,18]

In previous studies, the ability of a bacterium to live and proliferate within osteoclasts was reported. The research was carried out by adding *Staphylococcus aureus* as a bacterium that causes osteomyelitis into osteoclast cultures. Osteoclast cells accommodate the intracellular growth and replication of bacteria in the presence of Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) and several other factors such as Nuclear Factor of Activated T-cells (NFATc-1) and Nuclear Factor kappa B (NF-κB). The results of this study indicate that osteoclasts are target cells of *S. aureus* and serve as sites for bacterial replication.[19] Periodontitis

and osteomyelitis have in common that there is massive bone resorption by osteoclasts, which is triggered by bacteria.[14,19]

It has been known through several research results that *P. intermedia* is involved in the process of alveolar bone destruction that occurs in periodontitis.[12,20] Differences and variations in experimental protocols, culture methods, and target cells were observed from various studies on *P. intermedia*. Consequently, it is crucial to identify the mechanism of bone damage caused by *P. intermedia* by systematically analyzing the published studies to provide valid evidence that would benefit future research on the prevention of alveolar bone loss.

Methods

Literature Search Strategy

The literature search was conducted on two electronic databases, PubMed and Scopus, using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.(21) The search on the electronic database used a combination of keywords, namely "*Prevotella intermedia*" OR "*P. Intermedia*" AND "bone" OR "bone loss" OR "bone destruction" OR "bone resorption" OR "bone formation" OR "bone remodeling" OR "osteoclast" OR "osteoblast" OR "osteocyte". Searches were limited to research published in the last ten years, using English, and in full-text articles. If, after searching, there was duplication of research between the two databases, then the duplication of research was excluded. The analysis of these studies was carried out from September 2020 to February 2021.

Literature Quality Assessment

After obtaining the selected articles, the quality assessment was done using the guidelines checklist from the previous studies.(22,23) The guidelines contain 11 items, which assess articles from title, abstract, introduction, methods, and results to the discussion. Each item has a score of 0 to 2, except for titles and objectives, which have a score of 0 to 1 (Supplemental Data 1).

Results

There were 901 studies identified by searching the electronic database after entering keywords, namely 105 studies from PubMed and 796 from Scopus. Searches in both databases use the filter feature so that the articles obtained follow the inclusion criteria. Research duplication from the two databases was then eliminated using the Endnote application. The number of

studies after eliminating duplication was 837 studies. The screening was conducted on 837 studies obtained in the previous stage by looking at the titles and abstract suitability.

Characteristics of Selected Literature

Research that met the inclusion criteria after searching with PRISMA guidelines was three studies, which were published in the 2010-2020 period. All selected articles are relevant to the research topic, which discusses the influence of *P. intermedia* on the mechanism of bone damage. The bacterial virulence factor analyzed in these articles is the LPS of *P. intermedia*. The articles discuss inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, IL-10, and PGE2. Of the three articles, there is one article targeting macrophages[24], one article targeting Human Periodontal Ligament Fibroblasts (hPDLs)[25], and the last article targeting human dental follicle stem cells (hDFSCs)[26]. Various methods were carried out to prove the influence of the virulence factor of *P. intermedia* bacteria on cells that have a role in the mechanism of bone damage. The details of this study are summarized in Table 1.

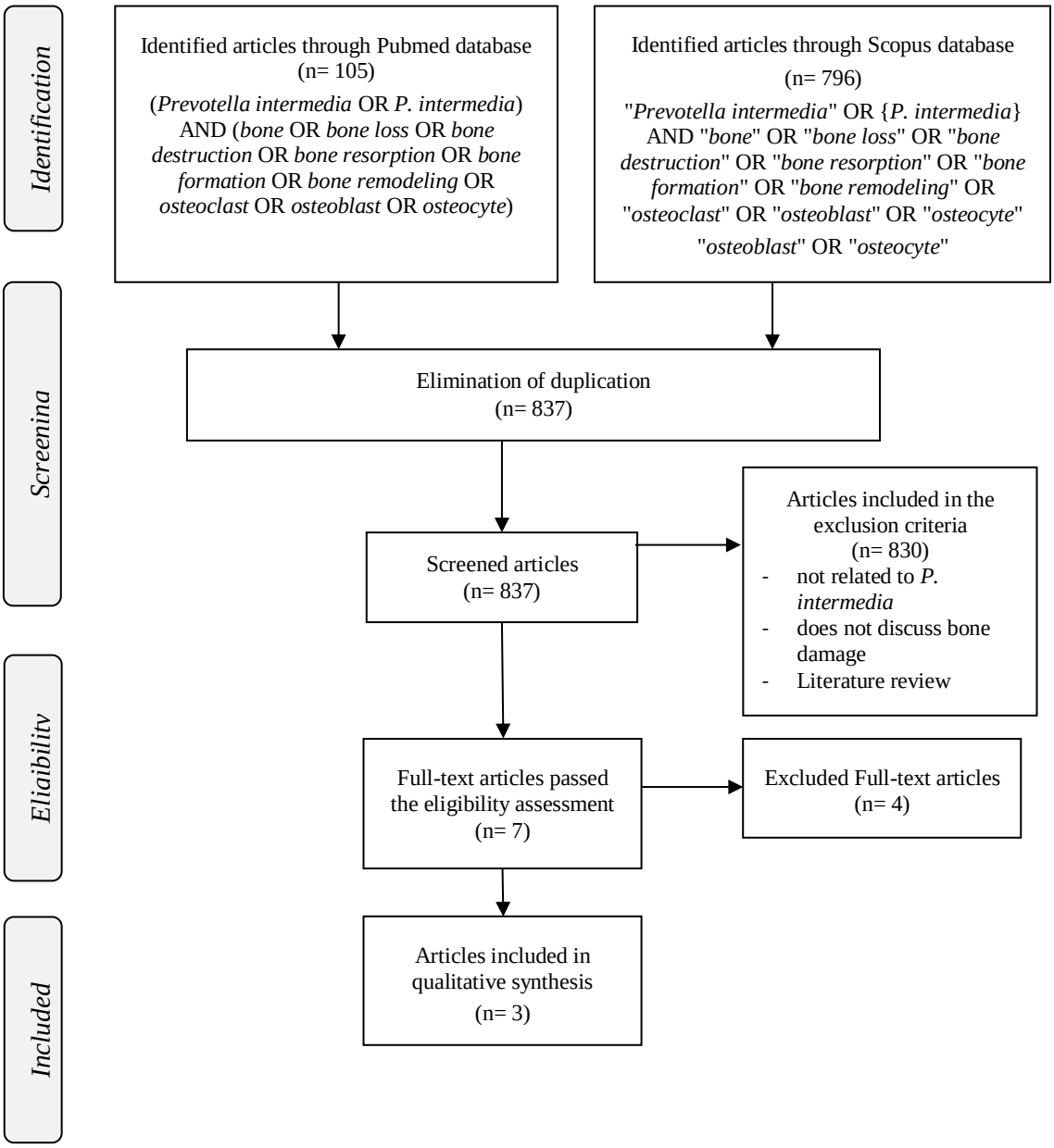

Figure 1. Flow chart of literature screening.

Table 1. Characteristic of the Eligible Articles

No.	Author	Bacteria/Virulence factor	Cell(s) Target	Molecule(s) Target	Methods	Results
1.	Kim et al., 2010	Lipopolysaccharide of *P. intermedia* ATCC25611	THP-1 macrophage cells	TNF-α, IL-8	1. ELISA was used to detect TNF-α and IL-8 in THP-1 macrophage cells treated with *P. intermedia* and leptin. 2. TNF-α mRNA levels were determined by semi-quantitative RT-PCR analysis	1. Increased production of TNF-α through leptin in THP-1 macrophage cells 2. leptin potentiated *P. intermedia* LPS-induced expression of TNF-α mRNA in a dose-dependent manner
2.	Guan et al., 2011	Lipopolysaccharide of *P. intermedia* ATCC25611 and ATCC49046	Human periodontal ligament fibroblasts (hPDLs)	PGE2, COX-1, COX-2	1. ELISA was used to measure *P. intermedia*-treated PGE2 secretion in hPDLs. 2. RT-PCR was used to detect COX-1 and COX-2 mRNA expression. 3. Western blot and immunocytochemistry were used to examine COX-2 gene expression.	1. Increased production of PGE2 in hPDLs. 2. Increased COX-2 gene expression but not COX-1. 3. *P. intermedia* in producing PGE2 is mediated by COX-2.
3.	Hieke et al., 2016	Lipopolysaccharide of *P. intermedia* ATCC25611	Human Dental Follicle Stem Cells (hDFSCs)	IL-6, IL-8, IL-10	1. Scratch assay was used to analyze cell migration in hDSFCs treated with *P. intermedia*. 2. ELISA was used to see IL-6, IL-8, and IL-10 in hDSFCs treated with *P. intermedia*.	1. *P. intermedia* were able to adhere and internalize into hDFSCs. 2. *P. intermedia* did not affect the differentiation and protein expression of stem cell markers (CD73, CD29, CD90, CD105, CD44 and CD45). 3. *P. intermedia* infection reduced the ability of hDSFCs to migrate under anaerobic conditions. 4. *P. intermedia* induces hDFSCs to secrete IL-6 and IL-8, but not IL-10. 5. *P. intermedia*-infected hDFSCs can reduce chemotaxis of PMN, reduce PMN's phagocytic activity, and reduce neutrophil extracellular traps (NET) formation in PMN.

Selected Literature Quality Assessment

The three included articles were assessed and scored according to the items provided in the guidelines. All articles have comparable total scores, of which the study from Guan et al. has

more detailed information on statistical analysis, and the study from Hieke et al. has a more informative background than the other studies.[25,26] Complete scores from the quality assessment are presented in Table 2.

Table 2. Quality Assessment of the Selected Literature

Studies		Item Score										
		1	2	3	4	5	6	7	8	9	10	11
LPS *P. intermedia*	Kim, et al. 2010	1	2	1	1	2	-	2	1	1	1	0
	Guan, et al. 2011	1	1	1	1	2	-	2	2	2	1	0
	Hieke, et al. 2016	1	2	2	1	2	-	2	1	2	1	0

Discussions

Infections from oral bacteria, including *P. intermedia,* have been well-documented to play a crucial role in the pathogenesis of periodontitis.[27–30] Mechanical cleaning and using antibiotics are strategies to maintain alveolar bone quality in patients with plaque accumulation or patients with a high risk of periodontitis.[1,31] The use of antibiotics has the risk of causing antibiotic resistance, which can have further medical consequences.[32] Therefore, inhibiting the invasion of pathogenic bacteria, including *P. intermedia,* without using antibiotics is the right step to avoid the uncontrolled use of antibiotics. Designing an inhibitor that can directly or indirectly bind to a peptide that increases the virulence of *P. intermedia* requires an understanding of the specific and detailed mechanism of action of *P. intermedia* on host cells. Through a systemic review of selected literature, it is hoped that a systematic and detailed description of the mechanism of action of *P. intermedia* on various cells that have been studied previously can be achieved.

P. intermedia is a main bacteria in the periodontal pathogen, often found in the periodontal pockets of patients with periodontitis. This present systematic review aims to determine the effect of *P. intermedia* on the mechanism of bone destruction in periodontitis. *P. intermedia* has various virulence factors, one of which is LPS. Of the three selected articles, all used LPS as a virulence factor in *P. intermedia*, with various target cells, such as macrophages, hPDLs, and hDFSCs. LPS is the main constituent of the outer membrane of Gram-negative bacteria. This virulence factor can trigger several host cells, especially mononuclear

phagocytes, to produce and release inflammatory mediators, including IL-1β, IL-6, IL-8, and most importantly, tumor necrosis factor alpha TNF-α.[24,33]

The first article by Kim et al. discusses the effect of leptin-treated *P. intermedia* LPS in inducing TNF-α in macrophages derived from THP-1 cell differentiation in human monocytic cell lines. Macrophages are the primary producers of TNF-α, which occurs in the connective tissue of periodontitis patients.[24] Leptin is an adipocyte-derived hormone that regulates food intake and energy balance. Apart from controlling body weight, leptin is also known for its role in inflammatory processes.[34]

Leptin is also classified as a cytokine because it has a tertiary structure similar to long-chain helical cytokines such as IL-6, IL-11, and leukemia-inhibiting factors.[35] The presence of leptin in the oral mucosa and salivary glands indicates that leptin activity is also crucial in diseases that affect the oral cavity. This study proved that there was an increase in TNF-α production in macrophages induced by LPS from *P. intermedia* assisted by leptin. However, no changes were found in IL-8 production, proving that LPS from *P. intermedia* that was given leptin affected the production of inflammatory cytokines, TNF-α.

TNF-α production has been recognized as a marker in various inflammation-related diseases. Evidence suggests that TNF-α plays a vital role in the pathogenesis of periodontal disease. TNF-α is abundant in the gingival sulcus fluid and gingival mucosa of patients with periodontal disease.[24] It has also been shown that TNF-α can induce connective tissue degradation and alveolar bone resorption. Furthermore, inhibition of TNF-α activity inhibited the inflammatory response and bone loss in primates in periodontitis experimental studies.[36]

The second article by Guan et al. discusses the *P. intermedia* LPS in regulating the production of PGE2 prostaglandins in hPDLs. Based on the results of this study, *P. intermedia* LPS induces PGE2 production in hPDLs. *P. intermedia* also increased COX-2 gene expression but not COX-1. COX-2 is the prominent COX that regulates PGE2 synthesis in the inflammatory response.[25] PGE2 has a role in the pathogenesis of periodontal disease by stimulating RANKL expression and downregulating OPG. Disturbing the balance of RANKL/OPG can also increase osteoclastogenesis. Furthermore, PGE2 upregulates IL-1α, which induces IL-6 expression, thus explaining its role in the inflammatory response.[37] Previous studies have shown that inhibition of PGE2 results in a significant decrease in matrix metalloproteinases and inflammatory cytokines that are induced by *P. intermedia*.[38] It can be

concluded that PGE2 is a mediator in the *P. intermedia*-induced inflammatory response in hPDLs.[25]

The third article by Hieke et al. discusses *P. intermedia* LPS in infecting hDFSCs and its effect on PMN activity. This study reported several results, including *P. intermedia* attaching and internalizing into hDFSCs.[26] Although there are few reports on the specific mechanism, type A fimbriae are thought to have relevance in internalizing *P. intermedia*.[37] *P. intermedia* infection in hDFSCs reduces the ability of cell migration under anaerobic conditions. The migration ability of cells is essential in the context of tissue repair and the repopulation of cells during wound healing.[39]

P. intermedia infection induces interleukin secretion by hDFSCs. In response to bacterial infection, cells can secret inflammatory cytokines to influence their environment. Research shows an increased accumulation of IL-6 and IL-8 but not IL-10. *P. intermedia* infection of hDFSCs reduces the chemotaxis and phagocytic activity of PMNs. During the first study, PMN was able to eliminate 75.5% of the presence of *P. intermedia*. However, in the presence of hDFSCs, the ability of PMNs to eliminate *P. intermedia* decreased to only 15.5% because there is a protective effect of hDFSCs on PMNs. In addition, internalization of *P. intermedia* into hDFSCs reduces the bacteria available for PMN phagocytic activity.[26]

Based on the results of the previous study, it can be concluded that the role of hDFSCs is like a double-edged sword because they can impair PMN activity and lead to better survival of periodontal pathogenic bacteria by maintaining sources of inflammation and immune responses. Hence, *P. intermedia* infection in hDFSCs preserves these cell functions while indicating a decrease in the PMN-mediated innate immune response.[26]

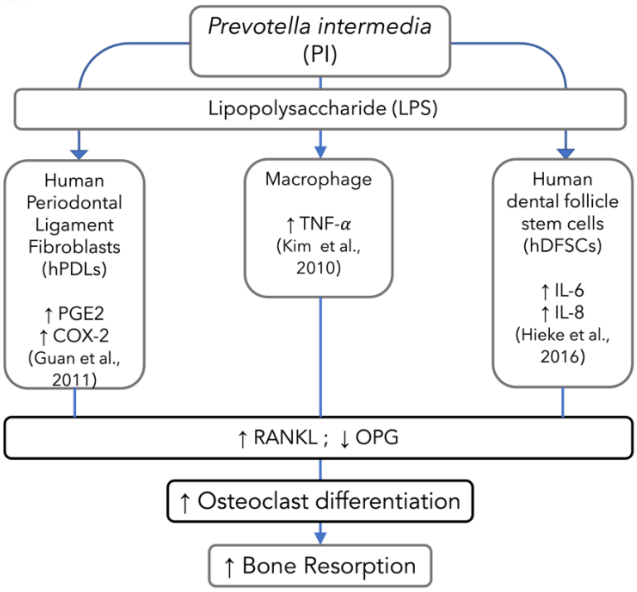

Figure 2. Mechanism of bone destuction by *Prevotella intermedia*. (PGE2: Prostaglandin E2; COX-2: cyclooxygenase-2; IL-6/IL-8: interleukin-6/8 ; RANKL: receptor activator of nuclear factor kappa-B ligand; OPG: osteoprotegerin; TNF-α: tumour necrosis factor alpha)

Conclusion

From the results of this systematic review, it can be concluded that *Prevotella intermedia* can increase the number of inflammatory mediators that play a role in the mechanism of bone damage, such as PGE2, TNF-α, IL-6, and IL-8 and their role in osteoclast activation and differentiation. However, no literature discusses the direct influence of *P. intermedia* on bone cells such as osteoclasts, osteoblasts, and osteocytes. Research on the association of *P. intermedia* with the mechanism of bone destruction is still very few, and most are more than ten years old. Further research that examines the direct interaction between *P. intermedia* and bone cells needs to be carried out and warrants further investigation.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary

Supplemental Data 1

Literature quality assessment form

Item	Description	Score
	Title and abstract	
1	Title: Accurate description of the contents of the article	(0): Not accurate (1): Accurate
2	Abstract: An accurate summary of the background, research objectives, methodology, main findings, and conclusions	(0): Not accurate (1): Incomplete (2): Accurate and complete
	Introduction	
3	Background: The available references are sufficient to support the motivation and content of the study	(0): Insufficient (1): Partly sufficient (2): Complete
4	Objective: The primary/secondary objective or hypothesis of the experiment is clearly defined	(0): Unavailable (1): Available
	Method	
5	Experimental Procedures: Detailed explanation of all procedures are provided	(0): Insufficient (1): Partly sufficient (2): Complete
6	Experimental procedure with animals (if any): Detailed explanation of animal use (animal species, developmental stage, status of genetic modification, number of animals used in each experimental group and trial allocation)	(0): Insufficient (1): Partly sufficient (2): Complete
7	Selection of procedures and materials are appropriate and accurate (molecular markers, evaluation of function, etc.)	(0): Insufficient (1): Partly sufficient (2): Complete
8	Statistical Methods: Details on statistical methods and analysis	(0): Insufficient (1): Partly sufficient (2): Complete
	Results	
9	Results: Detailed explanation on the results of each experiment	(0): Insufficient (1): Partly sufficient (2): Complete
	Discussion	
10	Interpretation: Detailed explanation of research results, study objectives, current theory, and other relevant studies	(0): Insufficient (1): Partly sufficient (2): Complete

11	Limitations: Brief comment on the limitations of the study	(0): Insufficient (1): Partly sufficient (2): Complete