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LL - 37 Cathelicidins and Beta Defensins in Periodontal Health and Disease

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Abstract: ***Background: Periodontitis is an inflammatory diseases affecting the tissues which support the teeth. Periodontitis is primarily caused by the interaction of plaque bacteria and immune responses. The host defence mechanism includes both innate and adaptive immunity. Antimicrobial peptide synthesis plays a critical role in innate defence mechanisms. Antimicrobial peptides (AMPs) are bioactive proteins that disrupt bacterial cell membranes, influence immune response, and regulate inflammation. Antimicrobial peptides effectively treat both Gram - positive and Gram - negative bacteria, fungi, and viruses. Human alpha - defensins (hADs), beta - defensins (hBDs), and Cathelicidin (hCAP18/LL - 37) are key antimicrobial peptides that help maintain the periodontal pocket and combat pathogens. Purpose: The aim of the present study was to conduct a literature search on the properties and effects of cathelicidin LL – 37 and beta – defensins in periodontal health and disease. Review (s): The main objective of the present literature search was to evaluate the effects of cathelicidin LL – 37 and beta – defensins in periodontal health and disease and to review the chemical and biological properties of cathelicidins LL – 37 and beta – defensins in periodontal health and disease. Conclusion: A total of 21 relevant papers and clinical trials were selected, and critically analysed as their data was extracted. Reviewing of the articles concludes that there is an increase in the levels of LL – 37 cathelicidin and human beta defensins in periodontal disease and it plays an important role in the host's innate immune response during periodontal inflammation. However, a significant drop in the amounts of LL - 37 cathelicidin and beta defensins was seen following periodontal therapy***

Keywords: LL - 37 Cathelicidins; Periodontitis; Human beta defensins;

1. Introduction

Periodontal disease (PD) primarily results from dental plaque biofilm, leading to the progressive deterioration of the periodontal apparatus. The periodontium is a complex tissue composed of the gingiva, periodontal ligament, and alveolar bone, providing mechanical and physical support to the teeth. Periodontitis is an inflammatory condition impacting the tissues that sustain the teeth.

Periodontitis can be caused by bacterial infections or pathogenic biofilms. Periodontitis development is heavily influenced by the interplay between plaque bacteria and immune responses (Kornman, 2008). According to Gorr (2009), the host's defence mechanism includes both innate and adaptive immune responses. Antimicrobial peptide production plays a crucial role in innate defence mechanisms.

Antimicrobial peptides (AMPs) are bioactive proteins that break bacterial cell membranes, modulate immunological responses, and regulate inflammation. These proteins are less than 100 amino acids and have molecular weights. Typically ranging from 3, 500 to 6, 500 Da. Antimicrobial peptides are effective against both Gram - positive and Gram - negative bacteria, fungi, and viruses (Dale & Fredericks, 2005).

Several salivary antimicrobial peptides, including alpha - defensins and beta - defensins, are expressed in the epithelium. The cathelicidin LL - 37 is expressed in both the epithelium and neutrophils (Dale Baer et al.). These peptides contribute to the host's innate immune response. Some of these peptides have anticancer, immunological modulatory, antibacterial, antifungal, and antiviral properties. Antimicrobial peptides play a role in the initiation and progression of periodontal disease, as well as immune - inflammatory reactions associated with risk factors like type 2 diabetes (Moreno - Navarrete et al.), smoking, psychological stress, and human immunodeficiency virus (Wang et al.).

During an infection, LL - 37 serves as a danger signal, connecting the innate and adaptive immune systems by directing immune cells such as monocytes, neutrophils, and T cells to the infection site (Nijnik A et al.). Dale BA et al. discovered LL - 37 in polymorphonuclear neutrophils (PMNs) in the undifferentiated junctional epithelium using antibodies and in situ hybridization techniques. The expression level in healthy individuals ranged from undetectable to 12 μg/ml, while it was elevated in patients with oral inflammation.

Gomez - Garces et al. found that LL - 37 is efficient against Aggregatibacter actinomycetemcomitans, which is the root of localised aggressive periodontitis. However, Porphyromonas gingivalis is resistant to LL - 37 in planktonic condition. In a 2023 research, Harini et al. found that β - defensin 1 protects T - Helper - 1 cells from P. gingivalis lipopolysaccharide - induced inflammation. β - Defensin 1 may be a new therapy option for periodontal infections. In 2023, Churen Zhang et al. concluded that HBDs are linked to immune infiltration in periodontitis. Vitamin D3 inhibits the generation of HBDs and chemokines from TNF - α/Pg - LPS in human gingival fibroblasts, perhaps through the NF - κB pathway.

Wael Abdulazeez Kzar stated that periodontitis elevates salivary LL - 37 levels in both smokers and nonsmokers, relative to healthy persons. These levels have a favourable correlation with periodontal parameters and can indicate periodontitis. However, smoking considerably lowers these levels.

Churen Zhang et. al concluded that HBDs are associated with immune infiltration in periodontitis. Vitamin D3 inhibits TNF - α/Pg - LPS - induced HBD and chemokine production in human gingival fibroblasts, presumably via the NF - κB pathway.

According to Mehmet taspinar et. al., A positive association was found between decreased HBD - 2, HBD - 3, calprotectin, and clinical periodontal indices.

Clinical periodontal therapy resulted in reduced systemic inflammation. Nonsurgical periodontal therapy for chronic periodontitis improves atherosclerosis prognosis.

The study conducted by Ana Elisa Rodrigu es it was found that individuals with periodontal disease had greater salivary concentrations of TNF - α and IL6, as well as lower levels of LL37. There was also an association between these chemicals and disease state.

The aim of the present library dissertation was to conduct a literature search and review the properties and effects and of cathelicidin LL – 37 and beta – defensins in periodontal health and disease which plays an important role synergistically and independently in maintaining oral health. Current research indicates that AMPs, including alpha - and beta - defensins and LL - 37, play a crucial role in sustaining oral health, both alone and synergistically. Innate immunity protects against oral pathogenic organisms by inducing the production of AMPs and regulating the amount of commensal bacteria. Understanding how bacteria control AMP expression gives insights into innate host defence in the oral cavity and potential targets for future therapies.

2. Review

History:
In 1939, Dubos discovered antimicrobial peptides (AMPs) by isolating an antimicrobial compound from a soil strain of Bacillus, which protected mice from pneumococcal infection. The first cathelicidin was identified in rabbit granulocytes as an 18 kDa precursor protein capable of binding to the bacterial endotoxin lipopolysaccharide. In 1995, the human cathelicidin protein was discovered and designated as hCAP18. The earliest reported animal - derived antimicrobial peptide (AMP) is defensin, which was isolated from rabbit leukocytes in 1956. In the subsequent years, bombinin from epithelial tissues and lactoferrin from cow milk were described. To date, 5, 000 AMPs have been discovered and synthesized.

LL - 37 cathelicidin:
Human cathelicidin LL - 37 is synthesised from hCAP - 18, a pro - protein encoded by the CAMP gene. Cathelicidin LL - 37 pro - protein is retained in neutrophil granules and epithelial cells until activated by proteinase 3, a serine protease. LL - 37 is believed to be released at the cell surface when neutrophils stimulate hCAP - 18, which may interact with an hCAP - 18 - specific receptor on the plasma membrane. LL - 37's microbicidal action primarily disrupts microbial membranes due to its cationic and amphipathic properties.

LL - 37 not only affects the innate immune system but also has immunostimulatory and immunomodulatory properties. Upon infection, LL - 37 works as a danger signal, bridging the innate and adaptive immune systems by attracting immunocompetent cells to the site of infection. LL - 37 regulates inflammatory cytokines, balancing the pro - and anti - inflammatory response.

Structure Of Cathelicidin LL - 37:
LL - 37 is a cationic amphipathic a - helical structure with three components, according to research using circular dichroism, Fourier Transform Infrared (FTIR), and NMR spectroscopy. The protein consists of an N - terminal a - helix, a C - terminal a - helix, and a C - terminal tail. The two helices are separated by a bend or break, depending on the membrane environment employed in the experiment. Cathelicidin LL - 37 interacts with negatively charged molecules and structures, including LPS, genetic material, and bacterial cell walls, thanks to its concave hydrophobic surface and positively charged residues. Cathelicidin LL - 37's hydrophobic surface is made up of four aromatic phenylalanine side chains pointing in the same way.

Cathelicidin LL - 37 In Oral Cavity:
LL - 37, a cathelicidin, is expressed in the human tongue, buccal mucosa, and salivary glands. It is found in the acinar cells of the submandibular gland and palatine minor glands, as well as in the lingual epithelium and palatal mucosa, following inflammatory stimulation. Immunohistochemistry studies revealed that LL - 37, derived from neutrophils, was detected in the junctional epithelium. It may also be expressed in the gingival epithelium.

Functions:
- Elevated levels of cathelicidin are commonly observed at inflamed sites, serving as a key defense against bacteria and other pathogens.
- Promotes quicker wound healing.
- Act as chemokines.
- The protective effect against Aggregatibacter actinomycetemcomitans, the causative agent of localised aggressive periodontitis, may be due to neutrophil movement across tissue rather than expression in epithelial cells.
- Antimicrobial activity against Streptococcus mutans, Porphyromonas gingivalis
- LL - 37 is capable of damaging Candida albicans' cell wall and membrane. It can also prevent the reproduction of smallpox virus. Furthermore, LL - 37 has antiviral efficacy against HSV – 1.

LL - 37: Antimicrobial activity:
Bacterial stimulation of neutrophils causes degranulation and release of cathelicidin LL - 37 into tissues. Bacterial metabolites from N. gonorrhoeae, E. coli, and Vibrio cholera may reduce cathelicidin LL - 37 levels in tissues other than

the mouth cavity. LL - 37 cathelicidin has a unique antibacterial effect that kills bacteria and neutralises gram - negative bacteria's lipopolysaccharide. LL - 37 binds to lipopolysaccharide - binding proteins or receptors, blocking lipopolysaccharide signalling and lowering inflammatory cytokines. A whole blood cytokine test showed that cathelicidin LL - 37 effectively neutralised lipopolysaccharide from P. gingivalis, suppressing inflammatory cytokines.

Regulation of LL - 37 in disease:
Cathelicidin LL - 37 levels in aggressive and chronic periodontitis are increased by F. nucleatum, P. intermedia, P. gingivalis, Tannerella forsythia, and Treponema denticola. Reduced cathelicidin LL - 37 synthesis is linked to periodontal disease, suggesting a unique role for cathelicidin LL - 37 compared to human neutrophil peptides. Cathelicidin LL - 37 deficiencies are linked to Papillon - Lefèvre syndrome and Haim - Munk syndrome. These conditions occur when the precursor cathelicidin fails to cleave the conserved pro - region of cathelicidin, resulting in activation.

Host immunity of LL - 37:
LL - 37 Cathelicidin inhibits cytokine expression when combined with bacterial products, but also increases production of cytokines linked to inflammation and chemotaxis.

Cathelicidin LL - 37 was shown to function synergistically with interleukin - 1 to increase the production of interleukin - 6, interleukin - 10, and monocyte chemotactic protein 1/monocyte chemotactic protein - 3 in human peripheral blood mononuclear cells. Cathelicidin LL - 37 acts as a direct chemoattractant, signalling through the G protein coupled formylpeptide receptor like - 1 on neutrophils, mast cells, T - cells, monocytes, and mast cells. Cathelicidin LL - 37 activates formylpeptide receptor like - 1 on endothelial cells, promoting vascular growth and repair. Cathelicidin LL - 37 plays several roles in the innate immune response, including preventing sepsis, inducing cytokines, recruiting cells, and promoting angiogenesis.

The sensitivity of periodontal tissues to LL - 37:
There was great heterogeneity among species and enhanced resistance to phagocytosis in the periodontopathic group, but no significant difference in sensitivity to LL - 37.

Separating bacteria into Socransky complexes, such as early colonisers (yellow/green/purple), orange and red complexes, and A. actinomycetemcomitans, revealed more distinct patterns. The red complex (P. gingivalis, T. forsythia, and T. denticola) exhibited the highest resistance to phagocytosis and LL - 37.

The role of the LL - 37 peptide in aggressive periodontitis, refractory periodontitis, and general periodontal diseases:
LL - 37 demonstrated pro - apoptotic action by increasing caspase 3 levels, whereas anti - proliferative activity was reached with an 8 M concentration. Surprisingly, assessed values strongly correlate with LL - 37 levels in GCF patients with chronic and severe periodontitis. Another research found that LL - 37 has a dual, concentration - dependent effect, promoting tissue and bone regeneration or wound healing while also causing destruction. Cathelicidin LL - 37 inhibits TLR ligand, lowers LPS - promoted osteoclast formation, and promotes angiogenesis and bone repair. LL - 37 inhibits Lipopolysaccharide - induced inflammation, promotes BMSC proliferation and migration, and stimulates osteogenic differentiation in both normal and inflammatory microenvironments through the P2X7 receptor and MAPK signalling pathway. However, it also contributes to BMSC destruction.

The LL - 37 peptide's role in safeguarding the mechanical properties of oral mucosa:
Recent research indicates that physiological failure during infection, inflammation, and carcinogenesis can result in structural changes in cells, organelles, and tissues. These alterations affect the rheological properties of biological structures. Tissue structural changes may be observed under a microscope, but mechanical alterations, also known as mechanomarkers, are more visible. The LL - 37 peptide's wide defensive qualities may help maintain normal oral tissue mechanics and prevent pathological alterations. The LL - 37 peptide enhances cell stiffness in epithelial cells by modifying their viscoelastic properties, a unique mechanism of action. Prolonged microbial colonisation alters cell and tissue dynamics, affecting transcriptional pathways in epithelial cell nuclei and raising cancer risk. LL - 37's antibacterial activity is believed to include interaction with the multicomponent lipid membrane, in addition to direct effects on bacterial cells.

The role of the LL - 37 peptide in oral mucosa diseases and its potential involvement in the development of oral cancer:
Pathogens that cause periodontal and pulp diseases, as well as mucosa diseases, may also contribute to pre - cancerous conditions and oral cavity cancers. For instance, P. gingivalis and C. albicans were found in the keratinocytes of patients with squamous cell carcinoma. Yeasts' role in oncogenesis has long been recognised, formerly connected to Candida's ability to produce nitrosamine. LL - 37 promotes autophagy of P. gingivalis in keratinocytes and influences TRIM22 and LAMP3 levels, preventing the development of neoplastic chambers.

LL - 37 affects cell wall remodelling in Candida albicans by reducing adhesion to surface cathelicidin, which binds to mannans and Xog1 exoglucanase. This activates the Mkc1 MAP kinase pathway and maintains wall integrity. LL - 37 promotes cell proliferation and decreases apoptosis, potentially leading to cancer development. LL - 37 has been linked to the development of oral submucous fibrosis (OSF), a chronic disorder with a high malignant transformation rate (1.5 - 15%), contributing significantly to death. Oral lichen planus is a chronic inflammatory disorder that may affect LL - 37 expression, although the aetiology is unknown. It is defined by the lysis of basal keratinocytes caused by immunological responses. Lichen planus patients have significantly higher salivary LL - 37 levels compared to healthy controls.

Beta – Defensins
Human defensins (hBDs) are minuscule, cationic AMPs found largely in epithelial cells and all epithelia. Beta - defensins are present in several epithelial tissues, such as

gingiva, skin, trachea, gut, Henle loops (kidney), salivary gland epithelial ducts, and pancreas. It was initially found in tracheal epithelial cells. The gingival epithelium expresses human beta - defensins in the top spinous, granular, and cornified layers, but not in the junctional epithelium.

Localization of Beta Defensins:
In cultured oral keratinocytes, hBD - 1 and hBD - 2 expression correlates with differentiation and is exclusively seen in involucrin - expressing cells. hBD - 1 and hBD - 2 were mostly identified in the granular and spinous cell layers. Despite frequent inflammation, hBD - 1 and hBD - 2 expression is not detected in the undifferentiated junctional epithelium of the oral cavity. The highest expression is found at the gingival margin, near plaque formation, and in inflamed sulcular epithelium.

Antimicrobial Activities Of Human Beta Defensins:
Human beta - defensin - 1 has modest activity against gram - negative bacteria, but human beta - defensin - 2 is extremely effective against gram - negative bacteria. Human beta - defensin - 3 is effective against both gram - positive and gram - negative bacteria, as well as Candida albicans.

Human beta - defensin - 3 is effective against bacteria in the red complex. All three antimicrobial peptides are active against A. actinomycetemcomitans, albeit with different interpeptides. Oral treponemes, including Treponema denticola, Treponema vincentii, and Treponema medium, are resistant to human beta - defensins 1–3. Human beta - defensins have antiviral activities against HIV - 1 and HSV - 1 viruses.

Defensin Expression During Inflammation:
Gingivitis is an inflammation of the gingival tissue caused by tooth plaque. Bacteria can quickly colonise the region, leading to additional inflammation. Periodontal pathogenic bacteria can increase the creation of AMPs, including human beta - defensins. RT - PCR analysis revealed that gingivitis - related tissues had lower levels of hBD - 1 and hBD - 2 gene expression compared to healthy gingiva. Gingivitis biopsies had mRNA for hBD - 1 and hBD - 2 in only 66% and 86%, respectively, but hBD - 3 was present in 100% of tissues. Periodontitis individuals showed lower levels of beta - defensin mRNA in their samples. Periodontitis patients had higher levels of hBD - 1 mRNA expression than healthy gingival biopsies, although less than 40% had both hBD - 2 and - 3.

Diverse oral bacteria exhibit distinct regulatory effects on human beta - defensins:
F. nucleatum, a commensal oral bacterium, up - regulated hBD - 2 without affecting other innate immune responses like IL - 8 production, which attracts neutrophils.

Bacterial LPS up - regulates hBD - 2 mRNA transcription in tracheal epithelia. However, LPS from P. gingivalis, F. nucleatum, and E. coli did not stimulate hBD - 2 in cultured GECs, indicating the involvement of signalling pathways beyond TLR4 activation. TLRs 2 and 4 play a little involvement in hBD - 2 activation by oral bacteria, suggesting that pathogenic bacteria may use a different signalling mechanism, such as PARs. hBD - 3 is found in both unstimulated and stimulated GECs and does not respond to P. gingivalis or PAR activators.

Beta defensins and their potential applications as therapeutic agents:
Hydroxychavicol, an extract from the Piper betle leaf, has been shown to suppress oral bacteria and may be used as an oral healthcare medication. Synthetic antimicrobial peptides offer potential for therapeutic uses, alongside natural ones from plants, insects, and humans.

B - Defensins In Periodontal Health And Disease:
In vitro studies using monolayer and multilayer cell culture techniques demonstrate that infection Inflammation affects hBD - 2 and hBD - 3 secretions, although hBD - 1 is secreted continuously. Furthermore, in multilayer models, the levels of hBD - 2 and hBD - 3 secretions coincide with the time spent incubation with microorganisms. Gingival samples from periodontitis patients and healthy controls were analysed. hBD - 1, hBD - 2, and hBD - 3 mRNA levels were lower in inflammatory gingival tissues compared to healthy ones. Protein levels differed between periodontitis patients and healthy people, with some slightly higher, equal, or lower. Several explanations have been proposed to explain the disparity. Common causes for reduced β - defensin expression include degradation by bacteria or host enzymes, as well as genetic variations (described below).

The first hypothesis is that during periodontal disease, the immune system replaces the innate response, resulting in decreased - defensin production. Beta - defensins are the first line of defence in the gingival epithelium, triggering an innate reaction to increased bacterial exposure. Immune cells take over the antibacterial function of - defensins as gingival lesions develop from early to established stages.

Bacterial colonisation leads to a rise in hBD 1 - 3 secretions, which can limit bacterial growth and biofilm formation. Bacteria resistant to - defensins, such T. denticola and P. gingivalis, thrive on epithelial surfaces before penetrating gingival tissues. During bacterial invasion, - defensins stimulate dendritic cell production of chemokines like IL - 8 and MCP - 1, which draw phagocytes and lymphocytes to the site of infection.

The second theory proposes that beta - defensins secreted during periodontitis are degraded by proteolytic enzymes produced by pathogens and the host. Periodontal infections can eliminate beta - defensins via destroying host peptides, among other means. P. gingivalis trypsin - like proteases and gingipains, for example, break down hBD - 1, hBD - 2, and hBD - 3. In addition to bacterial proteases, host proteolytic enzymes may help break down - defensins. Cathepsin B and L, cysteine proteinase enzymes produced by macrophages, rise in gingival tissues during periodontitis. In vitro, these enzymes may degrade and inactivate hBD - 2 and hBD - 3.

The third theory highlights genetic polymorphisms in beta - defensin genes. While beta - defensin expression and secretion do not decrease in periodontitis, individuals with low beta - defensin secretion due to particular genetic abnormalities are more likely to develop periodontitis. Previously, variations in hBD - encoding genes were linked

to bacterial carriage and disease activity. Type 1 diabetes and single - nucleotide polymorphisms in the hBD - 1 - encoding gene have been linked to higher incidence of C. albicans. Functional differences in hBD genes have been connected to the incidence of caries lesions. The link between functional polymorphisms in defensin genes and periodontitis susceptibility is probable, but has to be proven.

Bacterial Resistance Against B - Defensins:
Bacteria respond to - defensin challenges by constructing capsules, modifying cell envelopes, forming biofilms, or cleaving defensins. Porphyromonas gingivalis, a common periodontal infection, destroys hBD - 3 using gingipains, deactivating the peptide.

B - Defensins in Gingival Wound Healing
Beta - defensins help heal wounds and regulate the immune system. Wound healing involves four stages: inflammation, re - epithelization, granulation tissue formation, and tissue remodelling. During the re - epithelization phase, epithelial cells migrate, differentiate, and proliferate. Furthermore, hBD - 2 and hBD - 3, but not hBD - 1, stimulate keratinocyte migration and proliferation. In vitro studies indicate that hBD - 2 promotes intraoral wound healing.

3. Discussion

The gingival epithelium often maintains a healthy equilibrium in the oral cavity, despite the presence of both commensal and pathogenic bacteria, without causing clinical inflammation. Anti - microbial peptides, including alpha - and beta - defensins, and LL - 37 cathelicidines, contribute to oral health both individually and synergistically. LL - 37 regulates cellular processes, including migration, proliferation, and cytokine production. It exhibits wide antibacterial activity against both Gram - positive and Gram - negative bacteria.

Short peptides produced from LL - 37 have potential advantages over the full - length protein. They can neutralise pathogen - released endotoxins, boost immunological responses, and provide antibacterial characteristics. Beta - defensins in gingival sulcular epithelia can increase the penetration of dental plaque bacteria and their products into connective tissue, leading to gingival inflammation. Periodontal disease progression may be influenced by the balance of bacteria and host reactions, including the production and antimicrobial activity of hBD and LL - 37 cathelicidines. cytokines. It exhibits wide antibacterial activity against both Gram - positive and Gram - negative bacteria. Beta - defensins are crucial antimicrobial peptides in the first response to bacteria in gingival tissues. Furthermore, they play both pro - inflammatory and anti - inflammatory roles in the development of periodontal disease. Previously, it was believed that all hBDs served the same role in a coordinated manner. hBD - 1, a multifunctional antimicrobial peptide, can initiate and regulate the immune response in the gingiva. Beta - defensins have several functions in the periodontium, including defence and wound healing via rebuilding damaged epithelium.

Lower blood levels of 25 (OH) D were linked to reduced antimicrobial peptide expression in gingival and GCF tissues in individuals with gingivitis and chronic periodontitis, according to Batuhan A. and Bayirli et al.

According Overhage J et. al LL - 37 reduces bacterial adherence to the tooth surface by regulating quorum - sensing - dependent genes involved in biofilm production. It also reduces biofilm thickness by boosting bacterial surface motility.

A clinical investigation by Sol A et. al., found a connection between Actinomycetem commetans growth and severe periodontal disease in patients with neutrophil abnormalities or poor LL - 37 production. LL - 37 acts as an opsonin, making AA susceptible to phagocytic clearance by neutrophils and monocytes. LL - 37's ability to kill AA bacteria suggests it may play a role in aggressive periodontitis.

Puklo et. al., examined the GCF content of LL - 37 in healthy, chronic, and aggressive periodontitis patients and concluded that neutrophils are the primary source of LL - 37 in healthy periodontium, whereas in periodontitis patients, other cells besides neutrophils contribute to local production of LL - 3.

Wang Q et al. found that inflammation in the oral mucosa increases the concentration of LL - 37 in saliva, which promotes carcinogenesis. Inflammation is currently considered the seventh feature of cancers.

Vardar - Sengul S et al. found that aggressive periodontitis patients may have lower levels of human beta defensin - 1, making them more vulnerable to the disease. Lower levels of human beta defensin - 1 in the gingival epithelium may indicate gingivitis or advanced periodontitis.

A research by A. S. Ertugrul et al. found that individuals with diabetes mellitus have higher levels of hBD - 1 and hBD - 3 in their gingival crevicular fluid, which help destroy bacteria.

L. C. M. Costa et. al., stated that GCF levels of hBD - 1 was higher in periodontally healthy individuals when compared to individuals with chronic periodontitis. This suggests a potential protective role of hBD - 1 in the susceptibility to chronic periodontitis.

In a research by Kahena Rodrigues Soldat on the influence of smoking on beta - defensin protein levels in periodontal disease, it was shown that smokers had lower GCF hBD 1 levels and higher hBD 2 levels than non - smokers in diseased areas.

In a study by Ayla Öztürk et al., serum and gingival crevicular fluid levels of human beta defensin - 2 (hBD - 2) were evaluated in patients with chronic periodontitis. Higher levels of GCF hBD - 2 were associated with chronic periodontitis, while lower serum concentrations of hBD - 2 were associated with chronic periodontitis patients. The authors hypothesised that the host boosts hBD - 2 levels locally to fight periodontal infections and bacterial burden.

McMahon et al. found that 1, 25 di - hydroxy cholecaciferol increases the production of LL - 37 and TREM - 1, an innate immune regulator expressed on myeloid cells. This enhances

TLR - mediated antimicrobial responses and the production of proinflammatory chemokines and cytokines in response to bacteria and fungal infections.

Lin et al. found that overexpressing LL - 37 inhibited P. gingivalis internalisation in HaCaT cells in a dose - dependent manner.

4. Recommendations for Future Research

Future study should investigate the molecular mechanisms involving LL - 37, especially during regeneration. More study is needed to understand the molecular actions of LL - 37, including its antibacterial effects on planktonic and oral biofilm bacteria. Commercialising LL - 37 for local medication delivery in periodontal pockets. Investigating the application of human beta - defensin coatings on dental implants to prevent perimplantitis. Future studies on nanotechnology - based medication delivery using human beta - defensins are encouraged.

5. Conclusion

LL - 37 regulates oral cavity homeostasis by regulating inflammatory cytokine levels and their impact on dental tissues. It also promotes vascularization, mesenchymal stem cell differentiation and migration, and limits the impact of bacteria - derived inflammatory factors through bactericidal activities. LL - 37 boosts IFN signalling and induces antiviral responses in susceptible cells.

Combining LL - 37 - derived short peptides with existing anti - infection or anti - cancer medications might lead to novel treatment possibilities. ß - defensins serve as the initial line of defence in the gingival epithelium. They have both proinflammatory and anti - inflammation. The disintegration of antimicrobial peptides may have helped reduce periodontal disease. The coordinating process starts with the continual production of hBD - 1 in the oral and sulcular epithelium. In response to bacterial infection, the epithelial surface layers release hBD - 2. hBD - 3 synthesis starts in the basal cell layers and spreads to the surface layers as the infection proceeds. Beta - defensins in the periodontium may aid in wound healing by mending damaged epithelium, in addition to their defensive function. Antimicrobial peptides can improve periodontal regeneration by promoting fibroblast adhesion and proliferation on injured root surfaces.

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Conflicts of Interest
The authors declare no conflict of interest

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