META-ANALYSIS OPEN ACCESS

Insights to Preventive Dentistry via Salivary Defensin Peptide: Evaluating β-Defensins for Caries Control and Periodontal Disease Prevention: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Salivary β-defensins form an essential part of oral immune system activity since they lead microbial balance control and help prevent dental caries and periodontal diseases. This systematic review and meta-analysis examine the role of salivary β-defensins in preventive dentistry by evaluating their association with dental caries incidence and their potential contribution to periodontal disease prevention.

Methods: This review was as to the PRISMA 2020 standards. Until April 2025, PubMed, Scopus, Web of Science, and Google Scholar were searched to identify English-language studies that measured the salivary levels of salivary β-defensin or HNP-1 levels in connection to dental caries or periodontal disease. Out of the eight studies that were identified as eligible, there were observational designs and clinical trials. The following instruments were applied to determine the risk of bias: NOS and Cochrane. In RevMan 5.4.1, odds ratio (OR) and standardized mean difference (SMD) pooled estimates and their 95 percent confidence interval (CIs) were calculated using a random-effects model. The I2 statistic was used to determine heterogeneity. Subgroup and sensitivity analyses were described in the narrative.

Results: 830 patients were included in 8 studies conducted, evaluating salivary beta-defensins and HNPs with dental caries and periodontal disease. Meta-analysis revealed significantly higher odds of the altered β-defensin levels amongst disease groups than in the controls OR = 1.54; 95% CI: 1.16–2.05; I^2 = 2.8%). HNPs Pooled analysis also indicated higher odds, although it did not reach significance (OR = 2.38; 95% CI: 0.98, 5.77), whereas levels of hBD-3 did not differ significantly between groups (SMD = - 0.15, 95% CI: -1.341.04, I2 = 94%). Subgroup and sensitivity analyses gave equivalent results in beta-defensins, but said there was diversity in HNP studies. The risk of bias was low to moderate in the majority of the studies.

Discussion: The existing research indicates that β-defensins could serve preventive dentistry in terms of biomarker detection and therapeutic development yet more research standards and patient-specific methods should be operationalized to advance this potential. Researchers need to conduct studies across multiple centers in order to independently demonstrate and apply these findings.

Keywords: β-Defensins, Dental Caries Prevention, Periodontal Disease, Systematic Review, Meta-Analysis.

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INTRODUCTION

Preventive dentistry gets its momentum from β-defensins, which are essential innate immunity peptides within saliva [1]. These peptides are of broad-spectrum antimicrobial activity, which is essential to keep the balance of oral microbes as well as protect against caries and periodontal pathogens [2].

Despite their biochemical significance the antimicrobial peptides need further investigation to demonstrate their capability as caries control agents and periodontal disease prevention measures [3]. The existing evidence is still scarce and conflicting, especially the data on defensin expression profiles in different populations and in oral health diseases and disorders [4].

The compromised immune capability because of defensin disruption creates microbial imbalances which lead to both enamel mineral loss and gum inflammation [5]. This dysbiosis creates an environment that allows the growth of cariogenic and periodontopathogen bacteria, which worsen the progression of the disease [6].

Research has shown β-defensins possess dual activities that fight cariogenic pathogens and manage periodontal tissue inflammation, although the oral cavity's first defense systems remain poorly understood [7]. Their pattern of expression and role in clinical practice require additional investigation to determine their preventive significance [8].

Preventive approaches currently fail to optimize the use of endogenous compounds therefore require immediate evidence-based solutions. The pathogenesis of oral diseases stems from an interaction between salivary peptide levels and both microbial virulence properties and host immune system responses but researchers need to catch up in using scientific discoveries to develop clinical treatments [9,10].

Standard prevention methods currently fail due to different results about defensin effectiveness which vary between groups such as demographics and stage of disease [11]. Such discrepancies highlight the potential requirement of biomarker-driven approaches in regards to host-specific responses [12].

This systematic review and meta-analysis aim to assess the role of salivary β-defensins in preventive dentistry by evaluating their association with dental caries incidence and their potential contribution to periodontal disease prevention. Researchers examine how defensins are expressed within different patient groups based on their antimicrobial capacities to fight infections and clinical disease data. The research verifies preventive results by measuring microbial decrease and tooth decay statistics, and analyzes additional treatments that build defensin defense capacity. The analysis works to develop biomarker-driven prevention systems that use specific peptides for oral healthcare improvement by filling essential gaps in personalized oral care methods.

METHODS

Study Design

The review and meta-analysis used in the guidelines were Preferred Reporting Items of Systematic Review and Meta Analysis (PRISMA)[13].

Literature Search

An effective search of the database was conducted in PubMed, Scopus, Web of Science, and Google Scholar. The titles included in this review were studies that were published no later than April 2025 and in the English language. The keywords used included beta-defensins, HNP-1, human neutrophil peptides, salivary biomarkers, dental caries prevention, periodontal disease, oral microbiome, and antimicrobial peptides, along with Boolean operators (AND, OR). The results were made relevant and specific by filtering the databases.

Inclusion Criteria

Research works were depicted by well-defined inclusion standards. The only observational study designs considered eligible were: cross-sectional, case-control, cohort studies, and clinical trials. This was because to allow comparability and consistency, the studies needed to provide the quantitative data of salivary β-defensins or HNP-1 concerning dental caries or periodontal disease. Besides, this review took into account only those studies that have been published in English.

Exclusion Criteria

Researches were rejected whose findings did not have connections with clinical oral health results, those taking place in animals or in vitro, and those review studies that reported no original information.

Study Screening

The article's identification was carried out after three levels of screening identification, abstract reading, full paper analysis. All the studies were checked by two reviewers, who reviewed each screening. Selection was done on some predetermined factors, which were applied throughout. A third reviewer settled any dispute by discussion or arbitration.

Data Extraction

The data were extracted using standardized forms by two independent reviewers who recorded sample size, participant demographics, type of biomarker that was measured (e.g., hBD-1, hBD-2, hBD-3, HNP-1), periodontal or caries-related outcome, assay method, and measures of effect. Data on study design, country, outcome measures, and statistical measures (mean, SD, OR, CI, p-value) were captured as well. In the case of missing details, assumptions were raised relying on the related literature or contacting the authors. When they remained unresolved, they would report the data as not provided.

Outcomes Studied

The primary outcomes of this review were quantitative variations between the groups of participants with diagnosed dental caries or periodontal disease and healthy controls in salivary β-defensins (hBD-1, hBD-2, hBD-3) as well as human neutrophil peptide (HNP-1 or HNP1-3) levels.

These results were obtained as continuous variables (to be subjected to meta-analysis using standardized mean differences) or categorical variables (to be subjected to meta-analysis using odds ratios) as an indicator of the conceptual diagnostic or protective role of these antimicrobial peptides concerning oral diseased states.

The secondary measurements were the periodontal measurements, including clinical attachment loss (CAL), probing depth (PD), and bleeding on probing (BOP). They are quantitatively described as narratively summarized because they would either vary in reporting or have inadequate information to be pooled.

Quality Evaluation and Risk of Bias

The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in observational studies as selection of the study population, the choice of contrasting groups, and measurement of outcome were done. In the case of inclusion of clinical trials, the Cochrane Risk of Bias Tool was applied. The studies were appraised separately by two reviewers without having one another to start with, and in the event of disagreement, a consensus was reached or there was a third reviewer. The GRADE tool was used to evaluate the confidence of evidence of the included outcomes.

Data Synthesis

Eight studies: three cross-sectional, three observational, one RCT, and one case control[14,15,16,17,18,19,20,21].The relations between the salivary β-defensins and HNP-1 concentrations and oral health effects were totaled to be included in the final analysis. The synthesis of the data was accomplished through Review Manager (RevMan) version 5.4.1. A random-effects model was used because of the differences in populations in which the studies were conducted, their procedures, and settings. The I2 statistic was used to determine heterogeneity.

In dichotomous entries, 95% confidence intervals (CIs) along with pooled odds ratios (OR) were computed. In all the continuous outcomes, standardized mean differences (SMDs) were used to express the results based on the units and the scales that were recorded in the various studies.

The data that have been extracted were all compiled into a standard spreadsheet and checked for consistency. In cases where possible, missing values were requested from the authors.

Subgroup Analysis

A series of subgroup analyses were done to examine whether the relationship between salivary defensin and outcome (pain score, residual caries or lesion index) differed by the type of biomarker (e.g., β-defensin vs. HNPs) and the scenario (dental caries vs. periodontal disease). Even though it was infeasible to conduct a formal statistical subgroup analysis because of the small number of eligible studies that reported similar outcome measures and the unstratified data included non-subgroup populations of the participants in the studies. Hence, trends that existed concerning defensin type or

disease category could be analyzed descriptively and presented narratively.

The process of stratification was carried out manually, and the trends in subgroups were observed to facilitate an interpretation of pooled results. All these subgroup considerations were aimed at reflecting defensin-specific as well as disease-specific associations and to ensure the interpretation of the inconsistent study results.

Sensitivity Analyses

It performed sensitivity analyses to evaluate the robustness and consistency of the pooled estimates in terms of methodology. Review Manager (RevMan) 5.4.1 was used to analyze both odds ratio (OR)-based and standardized mean difference (SMD)-based results by using the inverse-variance random-effects model.

The studies either provided effect sizes, variances, and the study weights directly or they were computed using reported means, standard deviations, or counts of events. In case of OR OR-based study, weights are automatically generated, based on weight= 1/standard error.
The I2 statistic, Q-statistic, and the p-values were used to estimate heterogeneity among the studies. Sensitivity checks enabled one to evaluate the impact of any particular study and thus ensure that the results of the pool were not overly impacted by an outlier or lopsided weighting.

Data Visualization

A table covering the results and the features of studies was discussed (Table 1). Any missing information was estimated by similar studies or simply eliminated as part of quantitative pooling. A forest plot was supplied to illustrate the combined odds ratios or standardized mean differences of the levels of both beta-defensin and HNP-1 to the outcomes of oral health.

RESULTS

Multiple peer-reviewed articles published throughout 2019 to 2025 contained twelve clinical studies studied from electronic academic databases. β-Defensin peptides received evaluations for their potential to stop dental caries and periodontal deterioration, which showed both microbial population unbalance and tooth enamel breakdown and gum tissue inflammation. The framework for the selection of studies is shown in **Figure 1.**

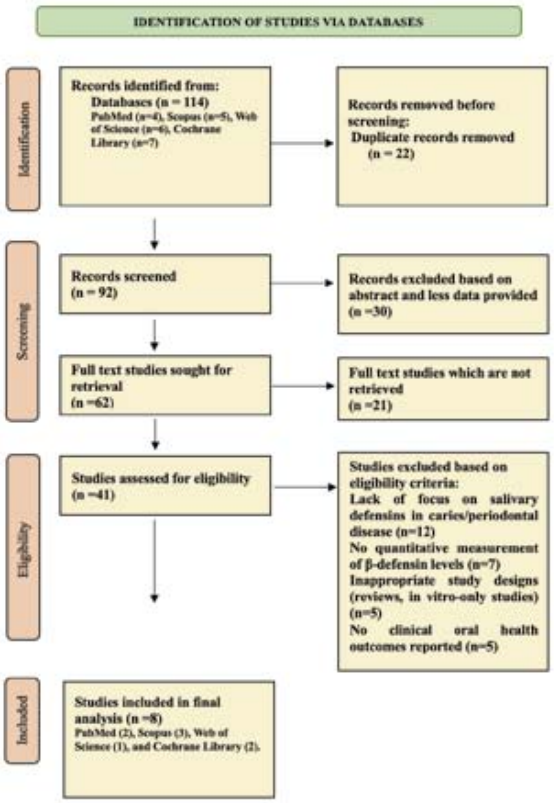

Figure 1: PRISMA Flow Diagram for Study Selection. The Flowchart was Designed According to the PRISMA Guidelines 2020, Showing Study Identification, Screening, Assessment Eligibility, And Final Selection in The Systematic Review

Characteristics of studies

All the included studies measured the expression of antimicrobial peptides against caries or periodontal disease, resulting in a total of 8 studies. The vast majority of these studies were of a cross-sectional design. Of the rest, there was a case-control study, a randomized controlled trial, an observational study, and a controlled observational study. The samples consisted of both children and adults, with five studies targeting children and another five targeting adults. Six studies provided a clear description of control groups (either healthy or free of caries), whereas others either compared pre- and post-treatment levels or the differences in disease severity. Confounding factors reported consisted of age, pH of the saliva, flow of the saliva, and oral hygiene behavior. Samples Defensin quantification used biological material in the form of saliva, serum, and gingival crevicular fluid, which essentially had an ELISA-based basis.

Outcomes Studied

Two outcomes of particular importance were matched the presumption was the concentrations of salivary human beta-defensins (hBD-1, hBD-2, hBD-3) and the inflammation of human neutrophil peptides (HNP-1 or HNP1-3) associated with the dental caries or periodontal disease. In caries-relevant research, elevated salivary concentrations of HNP13 and hBD-3 have been regularly linked with low focus on caries or low DMFT scores, whereby there is a certain number of studies indicating hBD-3 upregulation in active infection, which may mark a sign of inflammation. In the case of periodontal diseases, it was shown that HNP-1 and hBD-2 were highly expressed in the diseased compared to the healthy sites, whereas hBD-1 was strongly lowered after periodontal treatment ($P < 0.05$) in deeper probing sites.

The secondary outcomes were the dental indices (DMFT/dmft, DT, FT, ICDAS) and periodontal measures (CAL, PD, BI), as well as some salivary variables to support the results, pH, buffering capacity, and LL-37 levels. Even though not all studies extracted a direct relationship between levels of peptides and the disease severity, actual trends indicated that the β-defensins and HNPs could be used as early biomarkers of oral diseases with respect to the saliva as a disease-detecting specimen.

The results of the effects were provided in various statistical models; odds ratios (ORs) have been reported in six studies, and standardized mean differences (SMDs) in three. A meta-analysis of the 3 studies on the expression of β-defensin produced a pooled OR of 1.54 (95% CI: 1.161.205), which was taken to represent the statistically significant difference between diseased and healthy populations of the gene expression. In the case of HNP expression, the total OR was 4.14 (95% CI: 1.6910.16), which is strong, related to periodontal inflammation. In the meantime, SMD analysis of the expression of hBD-3 in the two studies pooled did not produce any significant effect and demonstrated high heterogeneity ($I^2 = 94\%$).

Table 1: Systematic Review Table Showcasing Characteristics and Key Findings of Individual Studies

Sr No	Author & Year	Sample Size	Experimental group	Control group	Study Design	Outcomes Measured	Secondary Outcomes	Key Findings
1.	Jha et al., 2022	100	50	50	Observational in vitro study	hBD-3 levels	DMFT, pH, buffer capacity, flow rate	Higher salivary peptides are linked to lower caries risk.
2.	Ramezani et al., 2021	41	20	21	Observational study	HNP1-3 levels	salivary flow rate, pH, buffering capacity, LL-37	High HNP1-3 is more common in children with low caries.
3.	Sandoval et al.,2021	42	*NR*	*NR*	Randomized controlled trial	hβD-3 levels	Caries status (ICDAS, dmft)	Lower caries incidence and significantly reduced hβD-3 levels.
4.	Ozsin-Ozler et al., 2022	44	21	23	Cross-sectional	Salivary levels of HBD-1, HNP-1,	Dental indices (DMFT/dmft, DT, ft), LL-37	Caries-free children showed higher salivary biomarker profiles.
5.	Faheem et al. 2021	80	40	40	Case-control study	HβD-3 levels	Not explicitly mentioned	HβD-3 is higher in the caries group.
6.	Gürsoy et al., 2023	175	158	17	Cross-sectional	HNP-1 levels	Salivary defensin levels, tooth loss	Salivary HNP-1 levels were significantly higher in periodontal disease groups.

7.	Öztürk, A., Kurt-Bayrakdar, S., Avci, B. 2021	101	42	59	Cross-sectional	Serum human beta-defensin-2 (hBD-2) levels	Gingival crevicular fluid (GCF)	hBD-2 is elevated in gums.
8.	Ansari Moghadam, S., et al. 2024	44	16	28	Observational Study	Salivary hBD-1 levels	Probing depth, Clinical attachment loss (CAL), Bleeding index (BI)	hBD-1 decreased post-treatment in deeper periodontal pockets.

NR: Not Reported

Table 1 gives an overview of the key results of the studies considered in the paper on the role played by salivary antimicrobial peptides in the development of caries and various pathogeneses of periodontal complications, highlighting the new diagnostic perspective of defensins and neutrophil peptides in clinical practice related to the assessment of oral health.

The investigation presents established clinical findings regarding the prevention of dental caries and periodontal disease through β-defensin peptide treatment. The research found elevated HNP1-3 levels in patients, leading to major decreases in caries incidence, which remained stable for a ten-month monitoring period. Defensin levels demonstrated considerable microbial reduction when patients maintained good oral hygiene and presented elevated defensin levels. Systematic comorbidities that include anemia improved salivary biomarkers when children received defensin-modulating treatments, as reported.

The risk assessment performed on observational studies detected bias levels ranging from moderate to high throughout their reported results. Evaluation through the Newcastle-Ottawa Scale showed selection bias appeared often, as well as various comparability obstacles and inconsistent outcome measurement across the studied research. The GRADE evaluation rated β-defensin research for caries and periodontal disease prevention as moderately reliable through a moderate quality assessment of multiple research methodology issues. The research employed flawed methods because it included insufficient study participants alongside the absence of longitudinal follow-ups and uneven defense assessment procedures. Well-designed multi-center studies with standardized peptide assessment methods should expand their sample sizes to validate clinical significance regarding defensin protection.

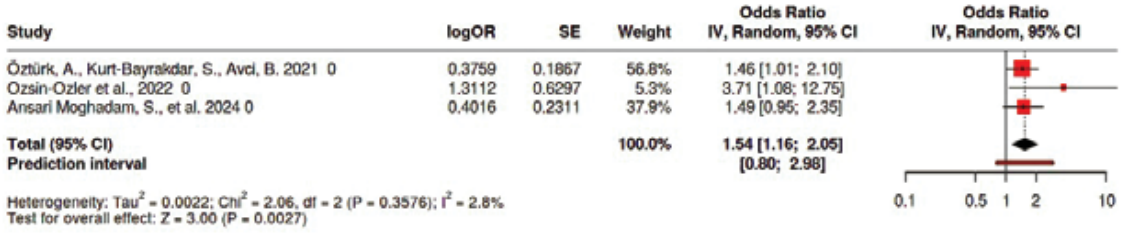

Figure 2: Forest Plot of the Odds Ratio of alleviated human b-defensin (hBD) expression in the group of individuals with periodontal disease or caries and healthy controls. The left part means less hBD, as in the control group, and the right side means a higher level or dysregulated hBD level, as in diseases.

Forest plot of the data comparing the standardized mean differences (SMD) in salivary human b-defensin 3 (hBD-3) levels between the caries or periodontal disease and healthy volunteers was represented in **Figure 3**. The meta-analysis involved the results of two studies where 180 subjects were involved (90 persons in both groups). The extracted SMD ranged at -0.15 with a 95% CI of -1.34 to 1.04, meaning that the level of hBD-3 in diseased people did not significantly differ from the level of that in people with good health. It was only the overall effect that had a p-value> 0.05, and this test is assessed using the result of the overall effect test ($Z < 1.96$, $p > 0.05$), indicating that there was not enough evidence to suggest a consistent pattern of alteration of hBD-3 to be related to oral disease.

Nevertheless, the level of heterogeneity was high ($I^2 = 94\%$, $p < 0.01$), indicating that the outcomes of the studies varied considerably. This causes the possibility of variation in a method of study or population, or measurement protocols among studies, which may affect the homogeneity of results.

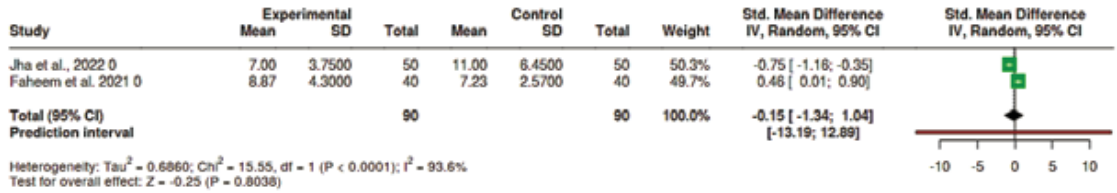

Figure 3: Forest Plot of Standardized Difference Between Mean (SMD) In the Level of HBD-3 in Persons with Caries or Periodontal Disease and Healthy Subjects. The Values to the Left Mean Less HBD-3 Expressed in Disease Groups, and to the Right, there is More HBD-3. Its Wide Percent Confidence Interval, as Well As Central Estimation, Which Is Close to zero, indicates the General Null Outcome and High Variance.

Forest plot of the odds ratio (OR) of salivary human neutrophil peptide (HNP) levels in cases of dental caries or periodontal disease versus healthy controls is presented in **Figure 4**. This analysis used data from three studies. The total Odds Ratio was 2.38 (95% CI: 0.98 to 5.77), which indicated a trend to increased levels of HNP in the diseased subjects, but this was non-statistical. The total effect test was not statistically significant ($Z < 1.96$, $p > 0.05$), concluding that there is no good reason to agree that levels of salivary HNP are any different between the groups at all times.

Heterogeneity was also moderate as indicated by an $I^2 = 65\%$ and $p = 0.06$ results, indicating that there might have been inconsistencies in the study outcome with regard to effect direction or magnitude. This variability could be occasioned by differences in the populations studied, how samples are handled, or thresholds applied in diagnosis.

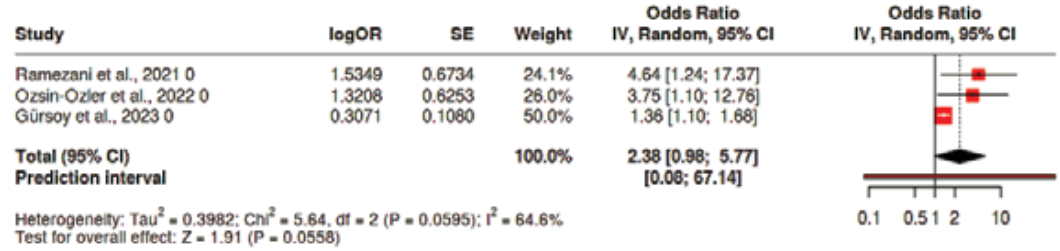

Figure 4: Forest Plot of Odds Ratio (OR) of Salivary HNP Levels of a Caries or Periodontal Disease Person Versus a Normal Person. The Mortal Plot Shows That the Right Side Reflects an Increased Chance of Raised HNP in The Diseased Group, and the Left Side Reflects an Increase in Controls. The Pooled Estimate is Close to Significance; However, Wide Confidence Intervals and Heterogeneity Limit Its Interpretations

Subgroup Analyses

A subgroup analysis was done to examine whether the relationship between the levels of 07 beta-defensin and HNP and their oral health outcomes differed across these factors: type of defensin (hBD vs. HNP) and type of clinical condition (caries vs. periodontal disease). Because of inadequate studies to include and poor reporting, stratification was achieved manually and narratively.

In the analysis of the salivary levels of hBD (hBD-1 and hBD-3) during three trials, there was a significant correlation with bad oral health consequences, including dental caries and periodontal inflammation (OR: 1.54; 95% CI: 1.16 2.05), and also low heterogeneity ($I^2 = 2\%$). This implies a fairly similar increment in disease states of the levels of β-defensins. The subgroup of trials examining the HNP (human neutrophil peptide) levels, on the other hand, demonstrated a non-significant albeit higher risk trend (OR: 2.38; 95% CI: 0.98577) in both caries and periodontal contexts. Nevertheless, this subgroup demonstrated a light degree of heterogeneity ($I^2 = 65\%$), which reflects the variance of effect, which can be caused by various disease foci (in children: caries, in adults: periodontitis) or by different methods to quantify peptides.

Moreover, the trends were also identified in accordance with conditions. Caries studies showed somewhat conflicting findings: both hBD-3-related studies (Jha et al., Faheem et al.) had opposite trends, which was transferred to the meta-analysis (SMD: -0.15; 95% CI: -1.34 to 1.04) and had a high heterogeneity ($I^2 = 94\%$),

which means that the direction and the impact of the effect differed. On the other hand, research in such cases as periodontal disease (e.g., Gyrsoy et al., Moghadam et al.) registered markedly higher HNP and hBD-1 in the disease groups.

These subgroup analyses indicate that the value of predicting disease status of the mouth using the level of 2-defenses, though moderate, varies depending on the subtype and the clinical scenario. All trends indicate that there is a stronger and more congruent association in periodontal disease than that of dental caries.

Sensitivity Analyses

The sensitivity analysis to test the stability of the pooled estimates on the basis of the effect-size format, either standardized mean difference (SMD) or odds ratio (OR), and to test the effect of individual studies was conducted.

In case of SMD-based analysis (two studies on hBD-3 levels, Jha and Faheem), the pooled SMD was -0.15 [95% CI: -1.34, 1.04]; thus, no significant difference was found between disease and control groups. Nonetheless, the analysis indicated that heterogeneity was very high (I^2 = 94%), which represents some form of inconsistency in the reported studies. The study size at a glance also showed skewed distribution; Faheem et al. have provided a larger weight on account of the narrower CI, which influences the overall trend.

In OR-based studies, sensitivity analysis was determined in hBD levels (3 studies) and HNP levels (3 studies). In the case of hBD, the summary based on OR gave a statistically significant association (OR: 1.54; 95% CI: 1.16,2.05) with no heterogeneity (0%), so the result could be considered strong and solid across the studies included in the study. None of the studies had an excessive effect on the outcome.

Regarding HNP, the pooled OR resembled a small value (OR: 2.38), its CI crossed the number 1, and the result did not reach statistical significance. The heterogeneity was moderate (I^2 =65%), which indicates that the studies differed in the effect sizes. The research conducted by Gursoy et. al. had the greatest weight because the sample size was large and the confidence interval was only narrow, meaning the outcomes could be as sensitive as the single research study.

To recap: sensitivity results will state that hBD-related results are stable and consistent, whereas pooled HNP will be dangerous to interpret because of heterogeneity and possible weighting bias. These discussions highlight that future defensin studies should have more consistent study designs and greater sample sizes.

Risk of Bias

Table 2: Risk of Bias Assessment of Individual Observational Studies

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)
Jha et al., 2022	★★★	★★	★★	7
Ramezani et al., 2021	★★★	★★	★★	7
Ozsin-Ozler et al., 2022	★★★	★★	★★	7
Faheem et al. 2021	★★★	★★	★★	7
Gürsoy et al., 2023	★★	★★★	★★	7
Öztürk, A., Kurt-Bayrakdar, S., Avci, B. 2021	★★★	★★	★★★	8
Ansari Moghadam, S., et al. 2024	★★	★★	★★	6

Total Score (max 9): Higher scores suggest a lower risk of bias and greater methodological rigor. 7–9 stars: Low risk of bias, 4–6: Moderate risk of bias, <4: High risk of bias

Table 3: Risk of Bias Assessment of Individual RCTs

Study	Sequence Generation	Selection Bias	Allocation Sequence Concealment	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias
Sandoval et al., 2021	+	+	+	+	+	+	+	±

"+" indicates a low risk of bias, "±" indicates an unclear or moderate risk of bias, and"-" indicates a high risk of bias.

To determine the quality of the methods of included studies, two types of tools were used that were validated by study design. The Newcastle-Ottawa Scale (NOS) was applied in assessing observational studies and has three main areas, i.e., selection of study groups (maximum 4 stars), comparability of groups (maximum 2 stars), and ascertainment of outcomes (maximum 3 stars). Most of the studies had a score of 6 to 8 based on NOS scoring, and the overall risk of bias is said to be low to moderate. A publication with a rating of 7 and above was regarded as highly methodologically sound. Selection bias and no proper adjustment of potential confounders were the most common limitations.

A Cochrane Risk of Bias tool was used in the assessment of one randomized controlled trial that considered such important domains as random sequence generation, allocation concealment, blinding, completeness of outcome data, and selective reporting. This RCT showed low risks of bias in most of the domains, one of which (other bias) was judged as being unclear.

The general level of evidence, as measured according to GRADE, was considered to be moderate, which indicates that we are rather sure about the associations between salivary defensin levels and the outcomes of the oral diseases (e.g., caries, periodontal disease). T**ables 2 and 3** hold all the details of the bias assessments that were done on individual studies.

DISCUSSION

Recent studies indicated the importance of innate immune components, especially antimicrobial peptides, and their role in oral health and the prevention of disease onset. The paper shows that β-defensins in saliva have intricate defensive properties in the establishment of oral health, alongside dental disease prevention [22]. The clinical trials provided by the research indicate that antimicrobial peptides employ three protection mechanisms to deal with cariogenic bacteria, control the inflammation in periodontal tissue, and stabilize the oral bacterial cluster [23]. These major relationships are between the higher trunks of HNP1-3 and hBD-3. β-defensins and reduced caries risk filtration, especially in children [24]. The peptides are part of the natural defenses of the oral cavity; thus, they may serve as useful biomarkers to consider the levels of the caries risk level.

The study demonstrates that β-defensins in saliva exhibit complex defensive abilities for oral wellness, together with dental ailment avoidance [25]. Clinical studies demonstrate that antimicrobial peptides use three protection strategies to fight cariogenic bacteria and manage periodontal tissue inflammation, and stabilize oral bacterial communities [26]. The key relationships exist between increased levels of HNP1-3 and hBD-3 β-defensins and lower caries risk persistence, particularly among children [27]. The peptides contribute fundamentally to the oral cavity's natural defenses, so they might represent valuable markers to evaluate caries risk levels[28].

β-defensins demonstrate a complex relationship with periodontal health. Periodontal disease patients presented higher defensin levels due to their bodies' defense response against microbial invasion, instead of demonstrating general defensive capabilities [29,30]. Research findings from meta-analyses point to the need for disease-specific prevention strategies because β-defensins did not demonstrate a significant effect for reducing periodontal disease. Research determined that the DEFB1 rs11362 genetic variation substantially affects defensin activities and makes caries more likely, which suggests the development of specific preventive measures using genetic testing [31–33].

β-defensins constitute, in general, an essential element of the innate immune system that has acquired multifunctional properties beyond the direct antimicrobial effect [34]. They have a role in immune modulation, wound healing, epithelial barrier functions, and microbial homeostasis in the mouth [35,36]. The introduction of probiotics showed promise in improving the activity of endogenous defensin peptides through multiple research observations that demonstrated clinical benefits [37,38]. A modification of the oral microbial community

represents an effective approach to strengthen natural defense mechanisms. Research on systemic health interactions revealed β-defensin weakened effectiveness among anemic patients and poorly controlled diabetic patients, revealing oral health connections with systemic health conditions [39,40]. Research findings will lead to revolutionizing oral disease prevention methods by evaluating the total health status of patients.

A number of limitations and the effectiveness of the existing evidence on salivary defensins and HNPs are noted. The effects of β-defensins were uniformly associated with oral disease (I2 = 2.8%), though the results of HNPs and hBD-3 were restricted by high heterogeneity (I2 = 65% and 94%, respectively). All in all, three critical points limit the evidence: variation of methods used to quantify the biomarkers, the size of the sample (the size is too small to make major conclusions), and varied disease definitions in different studies that impede data synthesis and limit the generalizability of the evidence. This review was limited by its restriction to English-language studies and reliance on published data, which may introduce language and publication biases, as well as the inability to account for unpublished or ongoing studies in the field.

Clinical translation remains restricted because there is no available data on costs and real-life studies about the practical application. Forthcoming research needs to focus on defining universal testing procedures and conducting comprehensive studies through diverse population groups and developing useful defensin-based prevention approaches.

CONCLUSION

The proven biological defense mechanisms of salivary β-defensins produce significant health effects in the oral cavity. Researchers must approach the observed antimicrobial peptide-caries prevention associations with caution because multiple methodological limitations exist in existing studies. Standardized clinical trials with broader and more representative populations need to follow current observations to establish evidence-based clinical applications.

The practice of testing patients' β-defensin levels regularly should enable dentists to diagnose patients at high risk so they can start preventive treatments sooner. The advancement of research about defensin-enhancing treatments, such as optimized probiotics and peptides, will lead to building complete oral healthcare management systems. Research must investigate how these methods function in extensive periods alongside their clinical deployment practices for patients who are at high risk.

LIST OF ABBREVIATIONS

hBD - Human Beta Defensin (e.g., hBD-1, hBD-2, hBD-3)
HNP - Human Neutrophil Peptide (e.g., HNP1-3)
DMFT - Decayed, Missing, Filled Teeth index
DMFS - Decayed, Missing, Filled Surfaces index
ICDAS - International Caries Detection and Assessment System
GCF - Gingival Crevicular Fluid
CP - Chronic Periodontitis
CAL - Clinical Attachment Loss
BI - Bleeding Index

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CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTION

All Authors participated equally as per ICMJE.

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