Review Article

Role of microRNAs in Diabetes-Associated Periodontitis: A Scoping Review

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ABSTRACT

Aim: Diabetes mellitus (DM), a metabolic disorder, exhibits a bidirectional relationship with periodontitis (PD), and recently, microRNAs (miRNAs) were associated with their progression. This review aims to assess the role of miRNAs in the pathogenesis of DM-associated PD and their plausible application as a biomarker for PD in individuals with DM. **Materials and Methods:** The search conducted until September 2023 on Medline (Pubmed), Scopus, Embase, and Web of Science using the keywords "microRNA," "miRNA," or "miR," combined with "Diabetes" and "PD" yielded 100 articles. Only research focusing on the role of miRNAs in the pathogenesis of DM-associated PD and their potential application as biomarkers for both conditions were included. Finally, 14 studies were assessed for any bias, and the collected data included study design, sample size, participant groups, age, sample obtained, PD severity, miRNAs examined, clinical and biochemical parameters related to DM and PD, and primary outcomes. **Results:** *In vivo* studies indicated altered expression of miRNAs-146a, -146b, -155, -200b, -203, and -223, specifically in the comorbid subjects with both conditions. Animal, *ex vivo*, and *in vitro* studies demonstrated altered expression of miRNAs-126, -147, -31, -25-3p, -508-3p, -214, 124-3p, -221, -222, and the SIRT6-miR-216/217 axis. These miRNAs impact innate and adaptive immune mechanisms, oxidative stress, hyperglycemia, and insulin sensitivity, thereby promoting periodontal destruction in DM. miRNA-146a emerges as a reliable biomarker of PD in DM, whereas miRNA-155 is a consistent predictor of PD in subjects without DM. **Conclusions:** miRNAs exert influence on immuno-inflammation in DM-associated PD. Although they can be biomarkers of PD and DM, their clinical utility is hindered by the absence of standardized tests to evaluate their sensitivity and specificity. Moreover, there has been limited exploration of the role of miRNAs in DM-associated PD through human studies. Future clinical trials are warranted to address this gap, focusing on standardizing sample collection, miRNA sources, and detection methods. This approach will enable the identification of specific miRNAs for DM-associated PD.

Keywords: *Diabetes mellitus, microRNA, periodontitis*

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Introduction

Periodontitis (PD) is a dysbiotic, polymicrobial, immunoinflammatory disease that impacts the supporting tooth structures, ultimately leading to tooth loss.[1] More than 500 microbial species, comprising five major bacterial complexes, colonize the deep subgingival pockets in PD.[2,3] These microbial species trigger complex innate and adaptive immune responses, establishing a link between PD and other systemic conditions, such as diabetes mellitus (DM), a metabolic disease and a significant risk factor for PD.[4,5] The relationship between the two is bidirectional, with individuals with uncontrolled DM having a threefold increased risk for PD compared to nondiabetics, attributed to progressive inflammation and oxidative stress.[5]

Elevated levels of deregulated systemic pro-inflammatory mediators, including prostaglandins, interleukins, metalloproteinases, and highly sensitive C-reactive proteins, contribute to periodontal destruction.[6,7] These upsurge oxidative stress and systemic inflammation, leading to endothelial dysfunction and cardiovascular diseases (CVDs) associated with PD.[6,7]

Early evaluation of specific biomarkers aids in diagnosing DM-associated complications as well as monitoring therapeutic outcomes, similar to N-terminal pro-B type natriuretic peptide (NT-proBNP), a biomarker released by cardiac myocytes. NT-proBNP facilitates early diagnosis, risk classification, and follow-up in CVD and heart failure.[7] Despite its levels being inversely related to DM risk, it serves as a biomarker for vascular complications.[8] Moreover, the reduction of NT-proBNP following full-mouth non-surgical periodontal therapy (NSPT) in PD is associated with improved cardiac parameters.[7]Similarly, transforming growth factor-β (TGF-β), another cytokine, promotes cell migration, proliferation, and differentiation while reducing pro-inflammatory cytokines such as interleukin-1, tumor necrosis factor-α, and metalloproteases, and TGF-β may serve as a biomarker indicating periodontal health.[9]

As inflammation is a common pathogenic attribute of both DM and PD, individuals with uncontrolled diabetics are at a higher risk of PD than those with controlled diabetics.[5] Alternatively, elevated levels of glycosylated hemoglobin in PD may contribute to the development of prediabetes or DM. In type 2 DM, effective periodontal therapy helps reduce glycated hemoglobin levels.[10] Nevertheless, the specific mechanisms linking DM and PD are only partially understood.

Recently, microRNAs (miRNAs) have emerged as biomarkers in type 2DM and associated complications, and they are related to the disease progression in both DM and PD.[11,12] Their altered profile has also been identified in the gingival crevicular fluid (GCF) of PD patients and chronic CVD associated with PD.[6] miRNAs are small non-coding RNAs with 19–24 nucleotides that regulate the expression of genes and have vital biological functions.[13] The mammalian genome encodes approximately 300 miRNAs, with each miRNA synchronizing several messenger RNAs, indicating their regulation of a significant portion of the transcriptomes and modulation of about 30% of genes in humans.[14-16] miRNAs influence the post-transcriptional expression of numerous genes and regulate both innate and adaptive immune responses, with cells selectively expressing over 100 miRNAs.[15,17] They are present intra- and extracellularly, with the extracellular miRNAs, stable in all body fluids, including saliva, being clustered in exosomes.[18]

Although miRNAs regulate insulin production, secretion, and action, chronic hyperglycemia modifies their expression profile, leading to early-stage DM.[11] In PD, miRNA dysregulation is induced by specific bacterial components in the dental plaque biofilm, which trigger immunoinflammatory reactions leading to the destruction of supporting periodontal tissues.[12] PD impacts the levels of miRNAs in periodontal tissues, leading to subsequent changes in their salivary profile. These miRNAs have the potential to serve as biomarkers of PD.[12] Similarly, genome-wide association reports have identified approximately 80 vulnerable loci for type 2DM, which are targeted by miRNAs expressed from islet cells.[19,20] As the dysregulated miRNAs trigger and promote DM and PD, this review aims to evaluate their role in the pathogenesis of DM-associated PD and their potential application as biomarkers for monitoring PD progression in DM.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) were followed in conducting this review.[21]

Review question

The review question was: Is there a role of miRNA expression in the pathogenesis of DM-associated PD?

Criteria for inclusion and exclusion of the studies

Observational case–control, cross-sectional, cohort studies, randomized controlled clinical trials, animal studies, as well as *ex vivo* and *in vitro* studies that investigated the role of miRNAs in DM-associated PD and their potential as biomarkers were included. However, case reports, reviews, and commentaries were excluded.

Search strategy

Up until September 2023, research publications on the role of miRNAs in DM-associated PD were identified by searching databases such as Scopus, Medline (PubMed), Embase, and Web of Science. Each database was searched using a combination of keywords such as "microRNA," "miRNA," or "miR," combined with "Diabetes" and "PD" in all fields without any year restrictions. After removing duplicates, two reviewers (RA and SG) evaluated the titles, abstracts, and full texts of the selected studies.

Data extraction

The information gathered from the included studies is as follows: study design, participant age, study groups, sample size, sample type, PD severity (mild, moderate, or severe), analyzed miRNAs, diabetic parameters, clinical and biochemical periodontal parameters, and primary outcomes [Tables 1 and 2].

Risk of bias assessment

To assess the possibility of bias, the National Institutes of Health's quality evaluation method for case–control studies, comprising 12 quality items, was used. A grading system of good, fair, or poor was applied.[35] Each item could be answered as "yes," "no," or "cannot tell," with a maximum score of 12 indicating good quality. Studies with seven or more "yes" responses were considered acceptable in quality. The included studies were graded as good quality as they demonstrated ≥9 "yes" responses [Table 3]. The risk of bias in animal research was evaluated using the SYRCLE tool, indicating a moderate risk of bias [Table 4].[36] Two reviewers (RA and SG) conducted this assessment independently and resolved any disagreements through discussion.

Results

Selected studies

There were initially 100 papers identified through the electronic search (28 in PubMed, 34 in Embase, 23 in Scopus, and 15 in Web of Science), with 53 duplicates removed. An additional 33 papers were excluded after reviewing the titles and abstracts of the remaining 47 papers for the following reasons:1 study involved women with gestational diabetes, 2 studies involved patients with COVID-19, 23 were not relevant to the search question, 2 were not in English, and 5 were literature reviews. Finally, the review included full texts of four *in vivo* studies in humans,[15,22-24] six studies in animals,[25,26,29,31,32,34] four *ex vivo* studies,[27,28,30,33] and two studies conducted *in vitro* experiments followed by assessment in animal models.[29,32] The study selection process is shown in the PRISMA-scR flow diagram [Figure 1].

Evidence from the *in vivo* studies in humans

All human studies were cross-sectional case–control studies.[15,22-24] For clarity, their results are summarized under four groups: Group 1 includes healthy subjects

Table 1: Studies reporting role of microRNAs in the association between DM and chronic PD

Author	miRNA analyzed	Main outcomes
Radovic *et al.*, 2018[22]	miRNAs •146a •155	• Upregulated miRNA-146a and miRNA-155, positively linked with SOD activity, positive association with PD, and plausible biomarkers for PD in diabetics and nondiabetics
Al-Rawi *et al.*, 2020[15]	miRNAs: •146 a •146 b •155 •203	• Salivary miRNA-146a and miRNA-155 are non-invasive, diagnostic, and prognostic biomarkers for periodontal health in diabetics and nondiabetics
Elazazy *et al.*, 2021[23]	miRNAs: •223 •200b •203	• In DM-associated PD, miRNA-223 and miRNA-200b are positively correlated, while miRNA-203 is negatively correlation with TNF-α • miRNA-203 is protective and promotes healing
Liu *et al.*, 2022[24]	miRNAs •223 •200b	• In DM-associated PD, increased expression of miRNA-223 and miRNA-200b in serum and GCF, which was positively associated with TNF-α, CAL, and PPD and negatively associated with IL-10

Table 2: Evidence from animal, *ex vivo,* and *in vitro* studies

Author	miRNA evaluated	Results and conclusion
Xu *et al*., 2016[25]	miRNA-147	• miRNA-147 promoted expression of the M1 phenotype in macrophages, increased levels of proinflammatory markers, and aggravated impaired glucose tolerance. Its inhibition shows promise in DM-associated PD.
Zhen *et al*., 2017[26]	miRNA-31	• Increased miRNA-31 in hyperglycemia impairs osteogenic differentiation of PDL stem cells and increases bone loss. • miRNA-31 inhibitors raise Runx2, Osx, and OCN expression, promoting bone formation.
Wu *et al*., 2017[27]	miRNA-126	• In human gingival fibroblasts, hyperglycemia lowers IL-10, increases TRAF6, IL-6, TNF-α, and chemical chemokine ligand-2 levels, and suppresses miRNA-126 expression. • By reducing TRAF6 mRNA and protein in human gingival fibroblasts, inhibiting the release of proinflammatory cytokines, and promoting IL-10, miRNA-126 mimics suppress inflammation, suggesting a promising treatment target for DM-associated PD.
Ou L *et al*., 2019[28]	miRNA-214	• Levels of receptor interacting serine threonine protein (RIP)-1, RIP-3, phosphor-mixed lineage kinase domain-like protein, and miRNA-214 levels were upregulated, while ATF4 decreased in inflamed gingival tissues of PD patients withDM. • In the inflammatory gingival tissues, RIP1 and RIP3 stimulated necroptosis, while miRNA-214 targets ATF4.
Li J *et al*., 2020[29]	miRNA124-3p	• Increased saliva Gal-3 in DM exacerbated alveolar bone loss. • In DM, alveolar bone is impacted by osteoblast-derived exosomes containing miR-124-3p, which controls osteoblasts' expression of Gal-3.
Monterio *et al*., 2020[30]	miRNAs-221 and 222	• Hyperglycemia increased hPDLCs apoptosis and caspase-3 protein expression through a reduction of miRNA-221 and -222 expression and elevation of caspase-3.
Byun *et al*., 2022[31]	miRNA-25-3p	• Insulin resistance increased salivary exosomal miRNA-25-3p in obese type 2 DM patients. • Considering that miRNA-25-3p targets CD69 mRNA, the administration of miRNA-25-3p inhibitors, which lower IL-17, may halt the inflammatory response and the activation of γδ T cells.
Li *et al*., 2023[32]	miRNA-126	• miRNA-126 prevented alveolar bone resorption in DM-associated PD and inhibited macrophage M1 polarization via regulating the MEKK2 signaling pathway.
He *et al*., 2023[33]	miRNA-508-3p	• hsa_circ_0084054 aggravates inflammation and promotes the progression of periodontitis in DM by regulating the miRNA-508-3p/PTEN signaling axis.
Li B *et al*., 2023[34]	SIRT6-miRNA-216/217 axis	• Reduced SIRT6 in macrophages exacerbates inflammation and periodontitis in DM. • Hyperglycemia disturbs the SIRT6-miRNA-216/217 axis.

without DM and PD; Group 2 (comorbid) comprises subjects with both DM and PD; Group 3 comprises subjects with only DM; and Group 4 comprises subjects with only PD.

Diabetic status of the participants evaluated in the studies

The subjects in the included studies were diagnosed with type 2 DM according to the World Health Organization (WHO) classification. In Groups 1 and 2, the DM participants had HbA1C levels <8%, ranging from 6.30% to 7.14%, respectively.[15,22] The fasting blood glucose (FBS) levels ranged from 96.81 to 113.76 mg/dL in Group 1 and 182.16–182.50 mg/dL in Group 2.[23,24] In Group 3, the HbA1C levels were between 7.01% and 8.22%,[15,24] and the FBS levels were 172.08 mg/dL.[24] Interestingly, participants in Group 4 had HbA1C levels ranging from 6.45% to 8.71%,[15,24] with FBS levels ranging from 102.60 to 172.44 mg/dL.[21,35]

Periodontal status of the participants included in the studies

The included studies assessed four clinical periodontal parameters: gingival recession, probing pocket depth (PPD), loss of attachment (LOA), and bleeding on probing (BOP). The WHO Community Periodontal Index was used to assess the periodontal status.[15,23] The plaque, BOP, and gingival indices were highest in Groups 2 and 4.[15,22-24] Participants exhibited mild to moderate or severe PD.[15,23] Across almost all the studies, LOA in Group 1 was the lowest, ranging from 1.21 to 2.24 mm, with PPD ranging from 1.21 to 2.17 mm. In the comorbid Group 2, LOA was highest, ranging from 5.16 to 8.87 mm, with PPD ranging from 4.79 to 5.88 mm. In Group 3, LOA ranged from 2.40 to 6.33 mm, and PPD ranged from 2.43 to 4.86 mm. In Group 4, LOA was between 4.92 and 6.35 mm, and PPD ranged from 4.42 to 4.90 mm.[22-24]

Table 3: Risk of bias assessment using the National Institutes of Health quality assessment tool of case–control study

Criteria	Radovic *et al.*, 2018[22]	Al-Rawi *et al.*, 2020[15]	Elazazy *et al.*, 2021[23]	Liu *et al.*, 2022[24]
1. Appropriate research question or objective	Yes	Yes	Yes	Yes
2. Specified study population	Yes	Yes	Yes	Yes
3. Sample size	Yes	No	No	No
4. Selection or recruitment of controls mentioned	Yes	Yes	Yes	Yes
5. Validation of cases and controls	Yes	Yes	Yes	Yes
6. Segregation of cases from controls	Yes	Yes	Yes	Yes
7. Random case and controls from appropriate participants	Cannot determine	Cannot determine	Cannot determine	Cannot determine
8. Concurrent controls were used	Yes	Yes	Yes	Yes
9. Confirmed that risk exposure occurred prior to the condition defining case	Yes	Yes	Yes	Yes
10. Clearly defined, valid and reliable, exposure/risk measures and implemented	Yes	Yes	Yes	Yes
11. Blinding of the exposure/risk assessors to the case or control	Unreported	Unreported	Unreported	Unreported
12. Measurement and statistical adjustment of the potential confounding variables	Yes	Yes	Yes	Yes
Quality rating:	Good	Good	Good	Good

Table 4: Risk of Bias assessment in Animal studies using SYRCLES's Tool

Type of bias	Xu *et al.*, 2016[25]	Zhen *et al.*, 2017[26]	Li *et al.*, 2020[29]	Byun *et al.*, 2022[31]	Li *et al.*, 2023[32]	Li *et al.*, 2023[34]
Selection bias •Random allocation	Yes	No	Yes	No	No	Yes
•Baseline characteristics reported	Yes	Yes	Yes	Yes	No	Yes
Performance bias •Blinding of the investigator	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Detection Bias •Blinding of the outcome assessment	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Attrition bias •Incomplete outcome reporting	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Reporting bias •Selective outcome reporting	No	No	No	No	No	No
Any other bias	No	No	No	No	No	No

Fluid or tissue investigated for miRNA sequencing

In the included studies, miRNA sequencing was conducted on samples obtained from saliva,[15] serum,[24] GCF,[22-24] and gingival biopsy using reverse transcription.[24] The forward primers used were hsamiR-146a-5p for miRNA146a, hsa-miR-146b-3p for miRNA146b, hsa-miR-155-3p for miRNA-155, and hsa-miR-203 for miRNA203. These miRNAs were reverse transcribed into cDNA and quantified using real-time polymerase chain reaction.[15,22-24]

miRNAs evaluated in *in vivo* human studies

The various miRNAs evaluated in the studies included miRNA-146a,[15,22] miRNA-146b,[15] miRNA-155,[15,22] miRNA-203,[15,23] miRNA-223,[23,24] miRNA-200b,[23,24] miRNA-106, and miRNA-103.[24]

The salivary levels of miRNAs-155,[15,22] -146a,[15,22] -146b,[15] and -203[15] were elevated in groups- 2, -3, and -4 compared to group 1. Similarly, the levels of miRNA-200b and -223 were significantly high in the serum, GCF,[23,24] and gingival tissue of these groups.[23] However, the comorbid group 2 exhibited the highest levels.[23,24] Similarly, Groups 2 and 4 demonstrated increased levels of miRNA-155 and miRNA-146b, alongside reduced levels of miRNA-146a and miRNA-203 in Group 2. Additionally, miRNA-203 was reduced in GCF, and the serum of Groups 2 and 4 was contrasted to Group 1.[23] Even though miRNAs-106 and -103 were expressed in the gingival tissue, their levels were

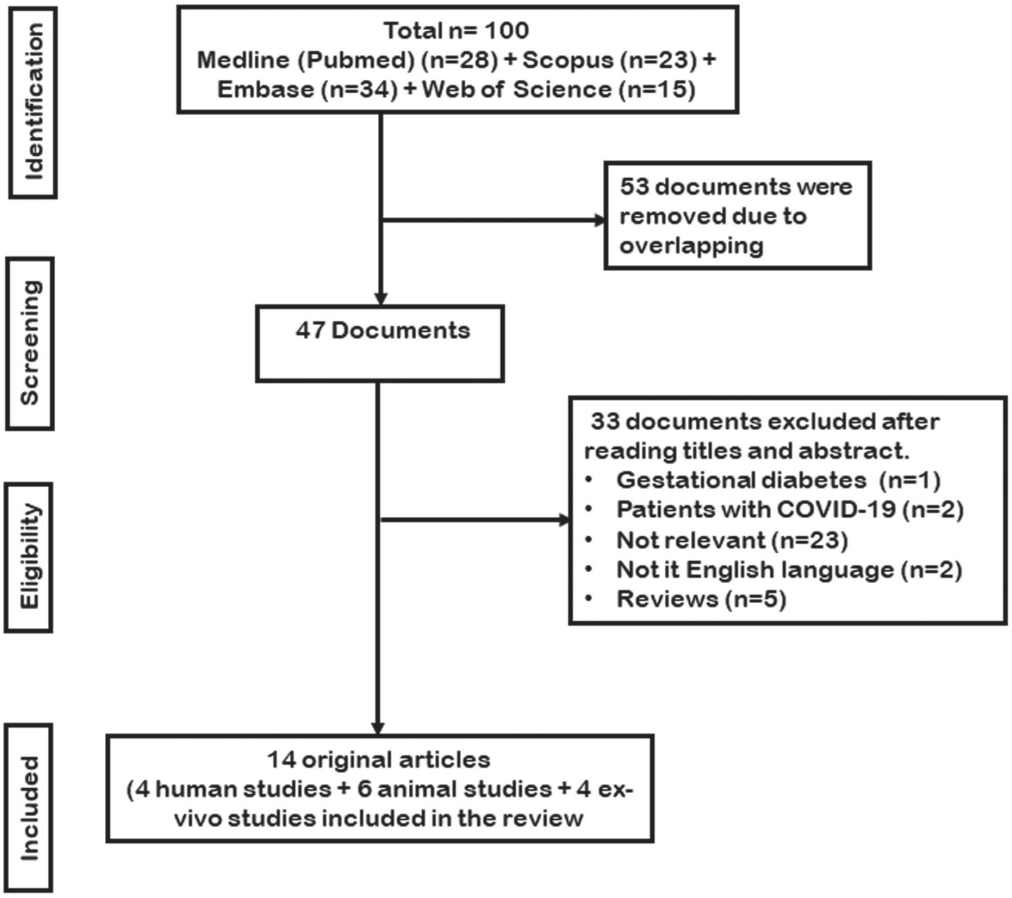

Figure 1: Evidence search for the role of miRNAs in diabetes-associated PD

insignificant.[24] Despite this, PD significantly increased the expression levels of miRNA-146a and miRNA-155 in GCF; however, their levels were reduced following NSPT and became comparable to Group 1.[22]

Target genes of the evaluated miRNAs *in vivo* human studies

The gene targets of miRNAs-146a, -146b, -155, and -203 are more abundant in CD56-positive natural killer cells, whole blood, CD4- and CD8-positive T cells, and islets cells of the pancreas.[15] Additionally, *in silico* analysis revealed that the mRNA of superoxide dismutase (SOD)-2 was targeted by a combination of miRNA-146a and -155, potentially leading to the silencing of SOD2 transcription.[22]

miRNAs as biomarkers for DM and PD *in vivo* human studies

The studies employed receiver operating characteristics (ROC) and area under the curve analysis to assess whether each miRNA could serve as a biomarker for discriminating PD with and without type 2DM and type 2DM in PD.[15,22-24] In Group 3 participants, three miRNAs, namely, miRNAs-146a, -146b, and -155, were significantly influenced by DM. The highest accuracy for predicting DM was observed for miRNA-155, followed by miRNA-146a, miRNA-146b, and miRNA-203. Additionally, only miRNA-146a predicted PD among subjects with DM. The miRNAs-155 and -146b predicted PD among nondiabetic participants. However, none of the miRNAs predicted DM in PD subjects.[15] In GCF, miRNA-146a and miRNA-155 exhibited high accuracy for PD in both nondiabetics and individuals with type 2DM. miRNA-146a demonstrated good sensitivity and specificity for detecting PD patients without DM. However, miRNA-155 outperformed miRNA-146a in individuals with type 2DM.[22] The serum miRNA-223 and miRNA-200b were able to significantly distinguish PD in individuals with type 2DM and nondiabetic subjects. However, all of the miRNAs in GCF, as well as serum miRNA-203, exhibited lower threshold values for differentiating PD with and without type 2DM.[23]

Alternatively, another study showed that the levels of miRNA-223 and miRNA-200b in the GCF could be utilized for diagnosing PD and the comorbidity of DM with PD.[24]

Association between miRNA levels in various body fluids with clinical and biochemical parameters *in vivo* human studies

Various biomarkers of inflammation such as TNF-α, IL-10,[23,24] and TGF-β were assessed in the serum, GCF,[23,24] and gingival tissue.[24] The levels of TNF-α[23,24] and TGF-β[24] were elevated, whereas IL-10 was lower in Groups 2 and 4 compared to Group 1.[24]

CAL, PPD, BOP, and TNF-α were positively associated with the GCF levels of miRNA-223 and miRNA-200b in Groups 2 and 4 and negatively correlated with IL-10.[23,24] Additionally, in both groups, miRNA-203 exhibited a negative correlation with TNF-α.[23] In Groups 2 and 4, both miRNA-146a and miRNA-155 showed a strong association with PPD. Additionally, their GCF exhibited elevated SOD activity, which was positively linked with the expression of miRNA-146a and miRNA-155.[22]

Evidence from animal studies, ex vivo, and in vitro studies

Various animal models conducted experiments in mice with induced type 2DM,[25,26,29] obesity,[25,31] and exposure to *Porphyromonas gingivalis* lipopolysaccharide (LPS)[29,32] or ligature-induced PD.[25,26,31,32] Additionally, salivary exosomal miRNAs were evaluated in type 2 DM and healthy subjects.[31] In a few studies, macrophages and human periodontal ligament cells (hPDLCs) were cultured to evaluate the role of miRNA in DM-associated PD.[26,30,32] Various miRNAs investigated in these studies were miRNA-126,[27,32] miRNA-147,[25] miRNA-31,[26] miRNA-25-3p,[31] miRNA-508-3p,[33] SIRT6-miR-216/217 axis,[34] miRNA-214,[28] miRNA124-3p,[29] and miRNA-221 and -222.[30]

The expression of miRNAs such as miRNA-25-3p, miRNA-147, miRNA-31, miRNa-508-3p, miRNA-124-3p, and miRNA-214 was elevated in the presence of high glucose and exposure to *P. gingivalis* LPS,[25,26,28,29,31,34] whereas the expression of miRNA-126,[27,32] miRNA-221, and miRNA-222 was reduced.[30]

Discussion

DM and PD influence miRNA expression and their effects can be cumulative. Microbial infections induce specific miRNA expressions that are upregulated time-dependently and negatively impact the host's innate and humoral immune responses. These include miRNAs in the immune and epithelial cells of human saliva such as miRNAs-155, -146-a, and b,[15,22] -200,[23,24] -203,[15,23] and -223.[23,24] Their influence on immune inflammation, oxidative stress, and insulin resistance will be discussed later.

Human chromosome 5q33.3 encodes miRNA-146a, whereas a gene 10q24.32 on chromosome 10 encodes miRNA-146b.[15] miRNA-155 is encoded by the host gene within the B-cell integration cluster region.[15] miRNA-223 is located on the X chromosome,[37] while miRNA-200b is present on chromosome 1p36.33.[38]

MiRNAs represent a continual inflammatory process in the periodontium because they are circulatory or exosomal components that persist in bodily fluids such as serum, saliva, GCF, and gingival tissues. They also play a role in immune regulatory processes and intercellular communication.[15,22-24,31,39] The studies showed that the participants had uncontrolled DM with mild to moderate or severe PD, with the most significant destruction in the comorbid group.[15,22-24] The levels of the miRNAs mentioned above were significantly affected in either DM or PD or both due to the following mechanisms [Figure 2].

Influence On Immuno-Inflammation In Diabetes-Associated Periodontitis

The nuclear factor kappa B (NF-κB) pathway induces miRNAs-146 and -155 when pathogen motifs, such as bacterial LPS, are sensed by pattern recognition receptors.[15,40] After the LPS challenge, miRNA-146a is expressed and plays a crucial role in innate immunity because it regulates the synthesis of cytokines. MiRNA-155 is anti-inflammatory as it regulates toll-like receptor-mediated (TLR) NF-κB activation and restricts inflammatory cytokine production.[15,40,41] The threshold for miRNA-155 activation by LPS is elevated in the presence of elevated miRNA-146a.[15,42] The NF-κB-miRNA-155 axis interacts with the NF-κB-miRNA-146a axis to regulate the intensity and progression of inflammation. The synergistic effect of these positive (NF-κB-miRNA-155) and negative (NF-κB-miR-146a) control loops optimizes NF-κB activity to mitigate inflammation.[15]

The cross-talk between miRNAs-155 and -146 mediates the regulation of inflammation. *P. gingivalis* LPS induces the overexpression of miRNAs 146-a and -b in gingival fibroblasts, subsequently enhancing the secretion of TNF-α, IL-6, and IL-1β.[43-45] Furthermore, miRNA-155 promotes the formation of atherosclerotic plaques, and its downregulation following NSPT may offer benefits in reducing CVD risk in PD and DM patients.[22,40]

miRNA-203 influences keratinocytes and regulates the cytokine signaling pathway in PD.[12,46] Studies have shown that it negatively correlates with TNF-α levels and suppresses inflammation.[15,23] miRNA-203

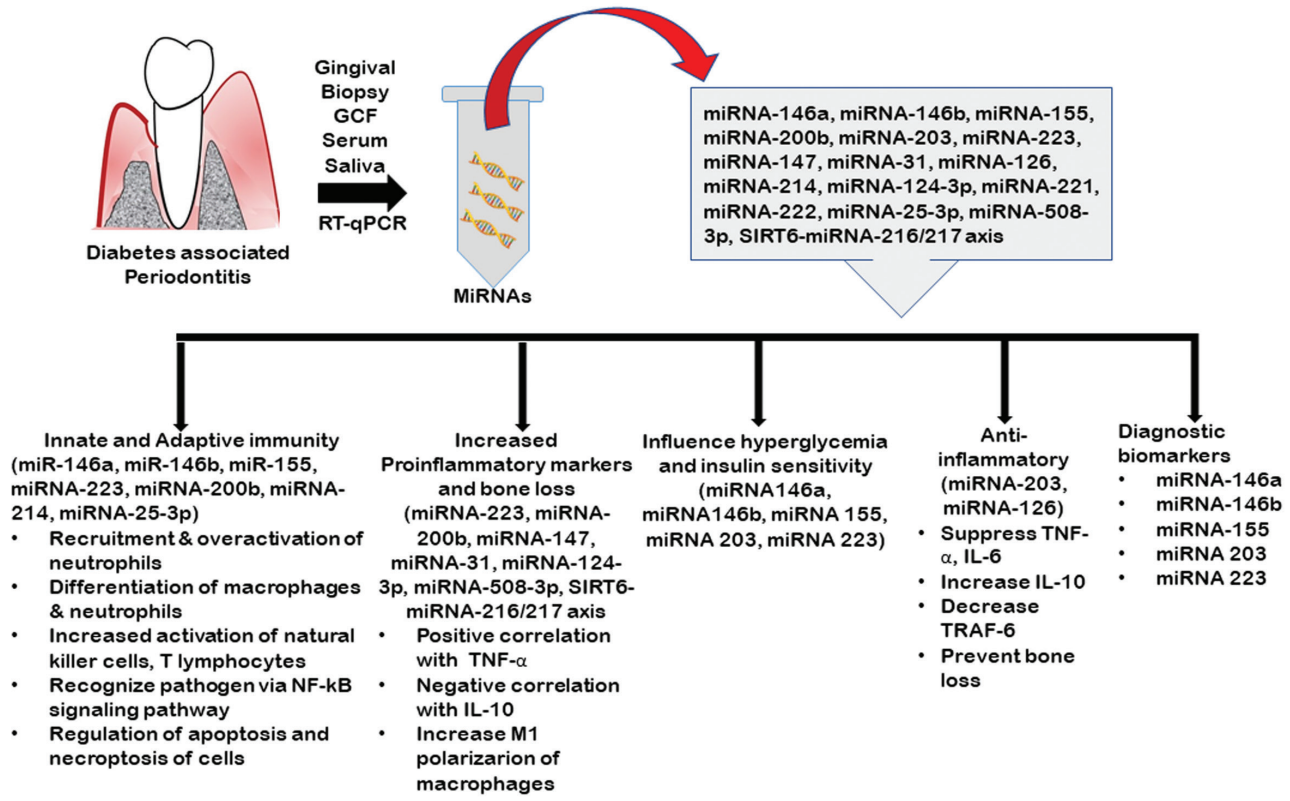

Figure 2: Role of miRNAs in diabetes-associated PD

is considered a protective factor and a therapeutic target for promoting healing in PD due to its role in promoting angiogenesis.[12,47,48]

miRNA-223 plays a crucial role in regulating innate immunity and tissue homeostasis, and it is involved in macrophage differentiation. Elevated levels of miRNA-223 have been observed in the gingival biopsies, serum, and GCF of patients with PD and DM.[12] This miRNA regulates neutrophil recruitment and contributes to alveolar bone loss by targeting nuclear factor1-A, inducing osteoblast death, and stimulating osteoclast differentiation.[12,23,24,49] miRNA-200b plays a role in promoting VEGF, which increases angiogenesis and vascular permeability in PD and DM. This miRNA is positively associated with the destructive cytokine TNF-α and negatively associated with IL-10.[23,24,50] On the other hand, MiRNA-25-3p suppresses CD69 in IL-17-producing γδ T cells, leading to periodontal inflammation and bone loss in obese mice with PD. This miRNA is found in higher abundance in the salivary exosomes of patients with type 2 DM.[51]

In the presence of high glucose and LPS in DM and PD, miRNA-147 is upregulated while miRNA-126 is downregulated. This dysregulation leads to increased expression of the M1 phenotype of macrophages and proinflammatory cytokines.[25,32] High glucose and LPS stimulate MEKK2-related pathways, such as NF-κB and MAPK, which induce this M1 polarization in macrophages. Conversely, miRNA-126 downregulates these pathways and inhibits M1 polarization of macrophages while promoting M2 macrophages, which reduce periodontal inflammation and alveolar bone resorption in DM-associated PD. Treatment with miRNA-126 mimics would be beneficial in this context.[32]

Increased glucose levels also diminish miRNA-126 expression in gingival fibroblasts, where it targets TRAF6. Hyperglycemia prompts the secretion of TRAF6, IL-6, TNF-α, and chemokine ligand-2, while reducing IL-10 production. Treatment with miRNA-126 mimics may aid in decreasing TRAF6 messenger RNA levels as well.[27]

In diabetic mice, elevated miRNA-31 expression was observed, targeting the Satb2 gene. Under high glucose conditions, transfecting PDL stem cells with Satb2siRNA inhibited their osteogenic differentiation, which was reversed by miRNA-31 inhibitors.[26]

Ex vivo research demonstrated that in DM-associated PD, activating transcription factor 4 (ATF4) decreased while miRNA-214, receptor-interacting serine-threonine protein (RIP)1, RIP3, and phospho-mixed

lineage kinase domain-like protein expression were elevated. RIP1 and RIP3 promoted necroptosis, with miRNA-214 targeting ATF4 and regulating osteoblast necroptosis in DM-associated PD.[28] Similarly, elevated hyperglycemia led to increased caspase-3 and decreased microRNA-221 and microRNA-222, inducing apoptosis in hPDLCs and delaying wound healing.[30]

Exosomal miRNA-124-3p derived from osteocytes regulates galectin (Gal)-3 production in osteoblasts during high glucose circumstances, exacerbating bone loss in DM-associated PD.[29] In both human and mouse models of DM, insufficient SIRT6 exacerbated PD due to the formation of apoptotic neutrophils and disruption of the SIRT6-miRNA-216/217 axis in macrophages.[34]

Influence On Oxidative Stress In Diabetes-Associated Chronic Periodontitis

Numerous chronic illnesses, such as DM, atherosclerosis, hypertension, myocardial infarction, cerebrovascular stroke, chronic renal disease, cancer, and PD, are linked to inflammation and oxidative stress. As the vascular tissue's first defensive response to harmful stimuli, inflammation often restores equilibrium by eliminating pathogens. However, prolonged dysregulated inflammation leads to tissue damage through oxidative stress, characterized by an imbalance in the oxidant–antioxidant response due to increased free radical production or activity or a weakened antioxidant defense system.[52] Since both PD and DM induce oxidative stress via an overactive innate immune system and an increased host immunological-inflammatory response, the presence of both conditions simultaneously exacerbates the imbalance in redox regulation, resulting in a compounding effect and more severe oxidative stress.[52,53] PD induces low-grade inflammation and creates oxidative environments characterized by reduced antioxidant capacity. Additionally, periodontopathogens stimulate the release of free radicals from neutrophils and macrophages. Phagocytosis is initiated when primed neutrophils bind directly or indirectly to the bacterium through the cell surface and Fcγ receptors.[52] This process leads to an oxidative burst, releasing excess oxygen free radicals that eliminate the microorganisms. However, tissue damage occurs due to the extracellular release of these reactive species. Reduced total antioxidants in PD result from the constant need for antioxidants to neutralize the exaggerated reactive oxygen species during periodontal inflammation. In DM-associated PD, hyperglycemia increases systemic and local inflammation in periodontal tissues. This is achieved by generating more complex glycation end products, disrupting the mitochondrial electron transport chain, and activating NADPH oxidase in a protein kinase C-dependent manner, all of which increase the generation of free radicals and intensify oxidative stress. These combined pathologic processes in PD and DM further exacerbate the observed periodontal damage.[52]

miRNAs-146 and -155 play a role in regulating oxidative stress in PD by controlling the expression of SOD-2 gene. SOD-2 is a mitochondrial antioxidant enzyme responsible for neutralizing superoxide anions to H_2O_2 and oxygen. The expression of miRNA-146a is induced by H_2O_2, which then suppresses the expression of the SOD-2 through a feedback mechanism.[22,54] Moreover, NSPT's ability to decrease SOD activity, inflammation, and the expressions of miRNA-146a and miRNA-155 suggests its therapeutic potential in addressing oxidative stress and inflammation in periodontal disease.[22]

Additionally, the elevated levels of the circular (circ) RNA has_circ_0084054 in the periodontal tissues of individuals with DM-associated PD indicate a potential role in exacerbating oxidative stress and inflammation. In PD patients with DM, it induces oxidative stress and inflammation by inhibiting AKT phosphorylation and upregulating the expression of phosphatase and tensin homolog through sponge miRNA-508-3p.[33]

Influence On Hyperglycemia And Insulin Resistance In Diabetes-Associated Periodontitis

In DM, overexpression of miRNA-146a downregulates TNF-α and the NF-κB pathway and prevents hyperglycemic complications.[15,55] However, the presence of PD in comorbid patients reduces its levels and decreases insulin sensitivity due to less effective inhibition of target genes involved in TLRs and cytokine production.[56] Similarly, miRNA-155 regulates blood glucose homeostasis and insulin sensitivity, and its overexpression improves glucose tolerance and insulin sensitivity.[57,58] Furthermore, hyperglycemia induces miRNA-203 expression, which delays wound healing in type 2DM.[59] The dysregulated miRNA-223 causes apoptosis of osteoblasts and endothelial cells, and elevated serum miRNA-200b levels in DM increase pancreatic β-cell apoptosis and promote DM.[23,49,60,61] Additionally, epigenetic mechanisms can alter miRNA-146a expression in GCF of type 2 DM patients, resulting in more severe periodontal damage in the comorbid group.[22]

Moreover, the findings from the included studies show that miRNAs-146a, -146b, and -155 were higher in PD with or without DM.[15,22] miRNA-146a can be

a reliable biomarker for PD in subjects with DM, whereas miRNA-155 was the most consistent predictor of PD in subjects without DM. Moreover, GCF levels of miRNAs -223, -200b, and salivary miRNA-203 may also be applied as markers for differentiating people with DM from nondiabetics and DM with healthy periodontium from those with both DM and PD.[15,23]

Although the above miRNAs may serve as biomarkers of PD and DM and help differentiate people with DM from nondiabetics and those with a healthy periodontium from those with PD, their clinical application is limited due to the unavailability of standardized tests to assess their sensitivity and specificity. Future studies should employ standardized sample collection protocols and explore miRNA sources such as serum, saliva, GCF, and gingival biopsy. Utilizing various detection methods will help ascertain precise miRNAs for DM-associated PD, whose expression levels may vary with disease progression or in response to treatment.

Conclusion

The present review highlights the impact of miRNAs on the innate and adaptive immune response, contributing to increased inflammation and bone loss in DM-associated PD. These miRNAs modulate immunoinflammatory pathways, increase oxidative stress, and exacerbate insulin resistance. Precisely, dysregulated expression of miRNAs-146a,-146b,-155,-200b,-203, and -223 in individuals with both conditions correlates with worsened periodontal health. Moreover, studies have demonstrated that miRNA-146a serves as a reliable biomarker for PD in DM, while miRNA-155 consistently predicts PD in individuals without DM. An in-depth understanding of the miRNA regulatory network could aid in diagnosing and monitoring related conditions. The levels of these biomarkers are altered in PD and DM, but they lack the specificity to discriminate inflammation caused by either of the two conditions. Therefore, further studies are required to validate the results of this review.

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Authors contributions

All the authors have contributed to the conception, article search, and manuscript writing. RA and SG assessed the titles and abstracts and evaluated the complete texts. All the authors were involved in data extraction and synthesis of results.

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Not applicable.

Patient declaration of consent

Not applicable.

Data availability statement

All data used to support the findings of this review are included within the article.

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Conflict of interest

There are no conflicts of interest.

List of Abbreviations

DM : diabetes mellitus
PD : periodontitis
CVD : cardiovascular diseases
NSPT : non-surgical periodontal therapy
NT-proBNP : *N*-terminal pro-B type natriuretic peptide:
TGF-β : transforming growth factor-β
miRNAs : microRNAs
GCF : gingival crevicular fluid
NF-κB : nuclear factor kappa B
TLR : toll-like receptor-mediated
RIP : receptor-interacting serine-threonine protein
ATF4 : activating transcription factor 4
hPDLCs : human periodontal ligament cells
Gal 3 : Galectin 3
SOD : superoxide dismutase
PTEN : phosphatase and tensin homolog

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