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Review Article

Salivary micro RNA as a potential biomarker in oral potentially malignant disorders: A systematic review

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Abstract

Oral potentially malignant disorders (OPMD) are oral mucosal disorders which have a high potential to turn into malignancy. A recent report suggests that 16%–62% of epithelial dysplasia cases of OPMD undergo malignant transformation, showing the need for early detection of malignancy in these disorders. Micro RNA (miRNA) plays an important role in cellular growth, differentiation, apoptosis, and immune response, and hence, deregulation of miRNA is considered a signature of oral carcinogenesis. A search was done using MeSH terms in the PubMed, ScienceDirect databases, hand search, and finally, six studies were included in this systematic review. A total of 167 patients with oral cancer, 78 with OPMDs, 147 healthy controls, and 20 disease controls were analyzed for the expression of salivary miRNAs. Quality assessment based on the Quality Assessment of Diagnostic Accuracy Studies 2 tool was used to obtain a risk of bias chart using Revman 5.3 software and it was proved that the study done by Zahran *et al*. in 2015 had a low risk of bias. The results of this study revealed upregulated miRNA 184 with an area under the curve (AUC) of 0.86 and miRNA 21 with an AUC of 0.73 and downregulated miRNA 145 with an AUC of 0.68, which proved that these miRNAs are significant in detecting early malignancy in OPMD and should be further analyzed in various populations. This systematic review explored the potential of expression of salivary miRNA in OPMD for future studies. This could pave the way to utilize saliva as a surrogate marker in diagnosing early malignant changes in OPMD.

Keywords: *Biomarker, Micro RNA, Oral cancer, Oral potentially malignant disorders, Salivary micro RNA*

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Introduction

Saliva contains a wide spectrum of proteins/peptides, nucleic acids, electrolytes, and hormones that originate from multiple local and systemic sources [1]. Salivary diagnostics is least invasive when compared to oral biopsy. The pathology in the oral tissues can be detected in saliva, as it contains the exfoliated cells from the immersed tissue. Salivary markers for the detection of malignant transformation of oral potentially malignant disorders (OPMD) are noninvasive diagnostic markers and should be analyzed for efficiency as surrogate markers. Saliva itself has proteomic, enzymic, and genomic markers of which Micro RNA (miRNA) is an upcoming marker [1,2]. MiRNA plays an important role in cellular growth, differentiation, apoptosis, and immune response, while some miRNAs aids in tumor suppression. During development of malignancy, some miRNAs are upregulated and some are downregulated, so any change in the expression of miRNAs can cause tumor suppression or act as carcinogens [3].

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Victor Ambros *et al*., Rosalind Lee and Rhonda Feinbaum were the first to discover miRNA [4]. Several hundred genes in our genome encode small functional RNA molecules collectively called miRNAs and are found in normal tissues, blood, and saliva. Initially, miRNA was found to be deregulated in systemic diseases such as diabetes [5] and hypertension [6] and was later found to be deregulated in ovarian [7], breast [8], colon [9], liver [10], and pancreatic cancer tissues [11]. During the process of development of oral cancer, certain genes acquire roles in tumorgenesis while some are tumor suppressors. Increased levels of certain miRNAs cause progression of malignancy while some suppress malignancy. Hence, they are considered human gene

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regulators as they are involved in gene transcription. *In vitro* studies on cell lines have proved the significance of miRNA as cancer signatures. Tran *et al*. in 2007 proposed from cell line studies of head and neck carcinoma that noncoding RNAs like miRNA play important roles in carcinogenesis [12]. Scully *et al*. proved clinical and histopathological assessment of OPMD is not sufficient to predict malignant transformation, hence, assessing the miRNA in these lesions would be helpful [13]. Cervigne *et al*. stated tissue expression of miRNA 21, miRNA 181b, and miRNA 345 is an early event in leukoplakia transforming into malignancy [14]. According to the WHO, India is the second largest consumer and third largest producer of tobacco, increasing the incidence of OPMD in India which demands the researchers to involve in studies to find diagnostic biomarkers in detecting early malignant changes in OPMD.

In this systematic review, various studies done in salivary miRNA as a biomarker for OPMD transforming to malignancy and in oral cancer were included in this study. Considering that there are few studies in this area, we focused on identifying the gaps in existing studies to suggest areas for future research on salivary miRNA as a potential target in detection of early malignancy in OPMD.

Aims and objectives

- To assess upregulated and downregulated miRNA in OPMD
- To analyze the most sensitive and specific miRNAs in detecting early dysplastic changes in OPMD
- To explore the potential role of miRNAs as biomarkers to detect early malignancy in OPMD.

Search strategy

For this systematic review, MeSH terms were used to search the PubMed data base, Science Direct and a manual search was done, and studies from 2005 to 2016 were included in this study. MeSH terms for key words (1) leukoplakia, ("Oral leukoplakia," "Oral leukoplakias," "leukoplakia," "leukoplakias," "leukoplakic lesions," "leukoplakic lesion," "lesion, Leukoplakic," "lesions, leukoplakic," "leukokeratosis," "oral leukoplakic lesions," "oral leukoplakic lesion," "oral leukokeratosis," "oral leukokeratoses," "oral keratosis") (2) oral submucous fibrosis (oral submucous fibrosis," "oral submucous fibroses," "submucous fibrosis," "submucous fibroses," "submucous fibrosis, oral," "submucous fibroses, oral) and (3) oral lichen planus (oral lichen planus," "lichen planus," "lichenoid eruption") along with salivary miRNA (mirnas" OR "mirna" OR "primary microrna" OR "pre m rna" OR "small temporal rna" OR "sirna" OR "pri mirna" OR "pre mirna" OR "primary mirna" OR "primary mi rna" OR "primary micro rna" OR "primary microrna" OR "rna, micro" OR "mi rna" OR "mirna" OR "micro rna" OR "microrna") and malignant transformation were used to retrieve studies on salivary miRNA in OPMD and oral cancer.

Selection criteria

Inclusion criteria

1. Studies on expression of salivary miRNA in OPMD
2. Studies on expression of salivary miRNA in oral cancer.

Exclusion criteria

1. Studies on expression of miRNA in serum, plasma, or tissues for both OPMD and oral cancers
2. Studies done on carcinoma other than the oral carcinoma were excluded from the study
3. Animal studies.

Around 574 articles were recovered from the web search, of which 197 were located after applying the human filter. Two articles were added from hand searching, for a total of 199. After applying the inclusion and exclusion criteria, 174 articles were excluded. Twenty four articles were obtained after screening the title. One article was excluded because the full text was not in English. Seventeen of the remaining twenty-three articles were done in tissue or serum samples of OPMD and oral cancer. A total of six articles, done in saliva samples of OPMD and oral cancer, were included in this systematic review [Figure 1].

Data extraction

The selected studies were evaluated by two editors after a data extraction table was developed. It captured the year of study, number of samples, and group methodology for the evaluation of miRNA, the place of the study, mean and standard deviation, cutoff values, sensitivity and specificity, and details related to statistical analysis [Table 1].

Literature evaluation

The number of samples analyzed for the expression of miRNAs in each case of OPMD and oral cancer is illustrated in Figure 2. One of the six studies was done only in OPMDs, two studies were done in both OPMD and oral cancer, and three studies were done only in oral cancer.

Quality assessment of the studies

The quality of these six studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool. This tool includes 14 items which assess the risk of bias and sources of variation in diagnostic studies. It is recommended by the Cochrane Collaboration, Agency for Health Care Research and Quality and the UK National Institute of Health and Clinical Excellence to assess the quality of diagnostic studies. QUADAS-2 is an improvised redesigned tool from the Cochrane Collaboration based on feedback from editors of the original QUADAS tool [15].

Risk of bias and applicability concerns

QUADAS-2 has four domains, patient sampling, index test, reference standard, and flow and timing. Each domain consists of two to four questions answered "yes," "no" or "unclear." This data were fed into Review Manager software (Revman 5.3) to obtain a color-coded chart of the risk of bias and applicability concerns [Figures 3 and 4]. The study of Zahran *et al*. had the lowest risk of bias of the six studies, while the three studies of Liu *et al*., Momen-Heravi *et al*., and AI–Malkey *et al*. had high risks of bias. The two studies of Park *et al*. and Hung *et al*. had moderate risks of bias. The low-risk bias study revealed upregulated miRNA 184 and miRNA 21 and downregulated miRNA 145 had statistically significant area under the curves (AUCs), proving the need for further focus on these

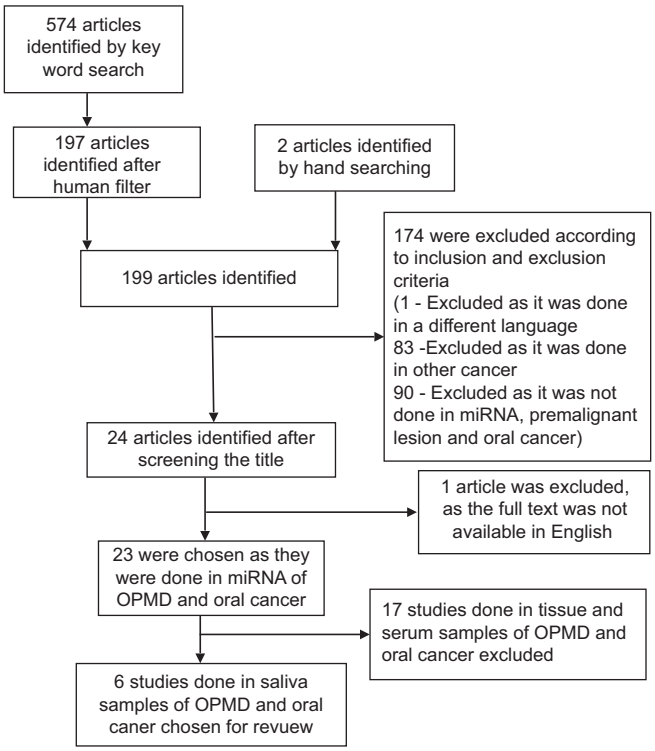

Figure 1: Prisma flowchart for selection of studies

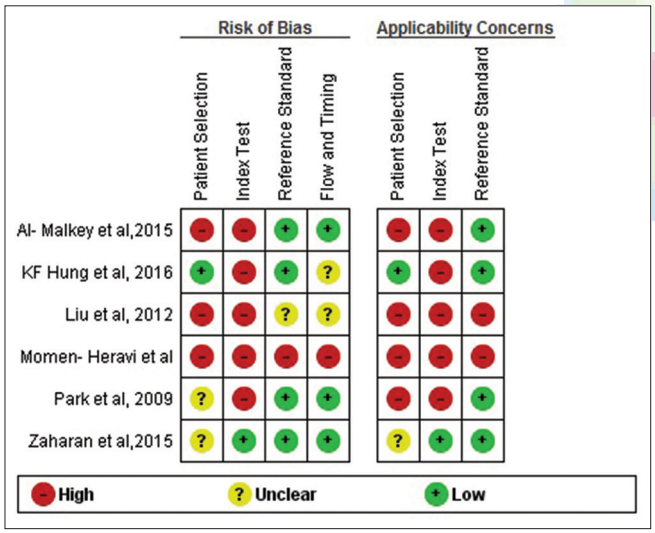

Figure 3: Risk of bias and applicability concerns for all six studies

markers in various populations in various dysplastic cases of potentially malignant disorders.

Discussion

Examination of saliva has emerged as a noninvasive technique in identifying various biomarkers for systemic diseases such as cardiovascular diseases [16] and diabetes [17] and oral diseases such as periodontitis [18]. In 2009, salivary miRNA was first investigated as a viable marker for oral carcinoma [19]. Various diagnostic studies on the expression of miRNA proved it was deregulated in the tissue [12,20-23] and serum [24,25] of patients with oral carcinoma.

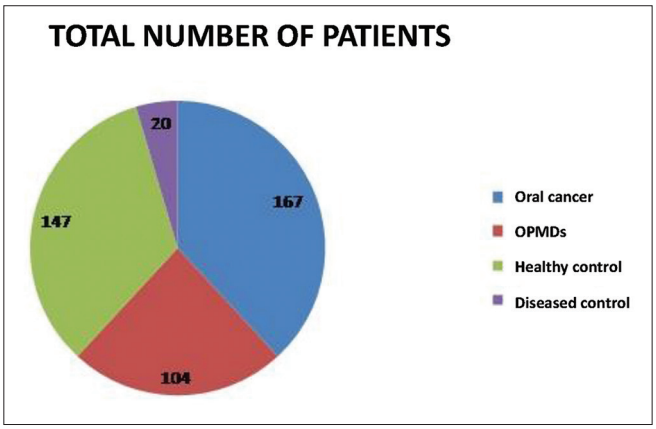

Figure 2: Total number of saliva samples evaluated for micro RNA

The studies in this systematic review mainly focused on the evaluation of the potential of salivary miRNA in diagnosing early malignancy in OPMD. Two studies by Momen-Heravi *et al*. and Zahran *et al*. proved miRNA 27b, miRNA 145, miRNA 181, and miRNA 21 had statistically significant sensitivity and specificity [Table 1] to detect early malignancy [26,27]. The study by Hung *et al*. mentioned the sensitivity [28], the study of Liu *et al*. mentioned only the specificity [29] and the studies of Park *et al*.[19] and Al-Malkey *et al*.[30] did not mention either the sensitivity or specificity of the markers.[Table 1]. Momen-Heravi *et al*. reported the overexpression of miRNA 27b and miRNA 24 in the saliva samples of patients in remission from oral squamous cell carcinoma (OSCC) [26]. Only one study, by Hung *et al*. in 2016, compared saliva samples with tissue samples and concluded that saliva samples were significantly better for predicting malignancy than tissue samples and miRNA 31 is a significantly better marker for predicting malignancy than miRNA 21 in saliva samples of OPMD [28].

A clear description of the saliva collection method was not given in one study [29] while in other five studies [19,26-28,30], unstimulated whole saliva was collected from the floor of the mouth, before which participants refrained from drinking, eating, and oral hygiene measures. RT-qPCR was used to quantify salivary miRNA in all studies [19,26-30].

These studies were done in saliva samples of 167 oral squamous cell carcinoma, 78 OPMD, 147 healthy controls, and 20 disease (aphthous stomatitis) controls. These studies proved that 5 miRNAs, miRNA-31, miRNA-24, miRNA-27b, miRNA-21, and miRNA-184, are upregulated and 15 miRNAs, miRNA-200a, miRNA-125a, miRNA-11, miRNA-191, miRNA-136, miRNA-147, miRNA-1250, miRNA-632, miRNA-646, miRNA-668, miRNA-877, miRNA-503, miRNA-200a, miRNA-323-5, and miRNA-145, are downregulated in OSCC compared with healthy controls [Table 1]. A total of 11 miRNAs that were deregulated in OSCC were also found to be deregulated in OPMD compared with healthy controls [25-28].

Only Zahran *et al*. compared disease controls (aphthous stomatitis) with healthy controls and found no difference between them [27]. Three studies found that miRNA 31 [28-30] and two studies found miRNA-21 [27,28] were elevated in OSCC.

Table 1: Data extraction of all six studies

Year, author, and population	Samples and method	Mean±SD	miR	Sensitivity, specificity, and AUC	Results
Park *et al*., 2009, 41 Caucasian, 4 Asians, 4 Hispanics, 1 African-American	50 - OSCC 50 - HC RT-preamp qPCR	miR-200a 28.7±3.9	Endogenous miR-191 Exogenous miR-124a miR-200a miR-125a	miR-200a Sensitivity and specificity not mentioned AUC - 0.65	miR-191 degrades at a lower rate than exogenous miR-124a miR-200a and miR-125a reduced in OSCC
Liu *et al*., 2012, Taiwan	45 - OSCC 10 - OVL 24 - HC RT-qPCR	miR-31-8.3±0.3	miR-16 miR-31	miR-31 Sensitivity - not mentioned Specificity - 100% AUC - 0.71	Levels of salivary miR-31 elevated in OSCC before treatment compared with normal saliva. Saliva of OVL showed no significant difference from normal
Momen-Heravi *et al*., 2014, Worcester, USA	9 - OSCC 8 - OSCC remission 8 - OLP 9 - HC Nano string miR expression assay and RT-qPCR	Not mentioned	Endogenous miR-191 miR-136 miR-147 miR-1250 miR-632 miR-646 miR-668 miR-877 miR-503 miR-200a miR-323-5p miR-24 miR-27b	miR-27b Sensitivity - 85.71% specificity - 100% AUC - 0.9643	miR 191 most stable hence selected as endogenous marker 11 miRs (miR-191, miR-136, miR-147, miR-1250, miR-632, miR-646, miR-668, miR-877, miR-503, miR-200a, miR-323-5) downregulated in OSCC, 2 miRs (miR-24, miR-27b) upregulated in OSCC 7 miRs which distinguished OSCC from OLP miR (over expressed-27b, under epressed-miR-146a, kshv-miR, Hcmv-miR-US5-2, Ebv-miR-BART16, miR-223, miR-29a)
Zahran *et al*., 2015, Jeddah, Saudi Arabia	20 - HC 20 - OPMD without dysplasia 20 - OPMD with dysplasia 20 - OSCC 20 - RAS qRT-PCR	miR-184-2.5±0.2 miR-21-3.7±0.2 miR-145-0.5±0.04	miR-184 miR-21 miR-145	miR-184 Sensitivity - 80% Specificity - 75% AUC - 0.86 miR-21 Sensitivity - 65% Specificity - 65% AUC - 0.73 miR-145 Sensitivity - 60% Specificity - 70% AUC - 0.78	miR-21 and miR-184 highest in OSCC followed by PMD without dysplasia, PMD with dysplasia, RAS, and HCs miR-145 lowest in OSCC
Al- Malkey *et al*., 2015, Baghdad, Iraq	35 - OSCC 20 - HC RT-qPCR	miR-31 26.4±16.7	miR-31 Cutoff value - 6.623 Inhibits negative regulators of cancer pathway and promotes cell proliferation	Not mentioned	Fold change was higher in oral cancer group than HC group
Hung *et al*., 2016 Taipei, Taiwan	46 tissue samples of OPMD 20 saliva samples of OPMD and 24 HC Tissue-*in situ* hybridization, saliva-qRT-PCR	Not mentioned	miR-21 miR-31	miR-31 Sensitivity - 100% AUC - 0.74 miR-21 Sensitivity - 100% AUC - 0.76	miR-21 and miR-31 significantly increased in saliva of OPMD. miR-31 and epithelial dysplasia significantly associated with disease progression. Neither salivary miR-31 nor epithelial miR-31 significantly increased in dysplasia epithelium

HCs: Healthy controls, OSCC: Oral squamous cell carcinoma, OPMD: Oral potentally malignant disorder, OVL: Oral Verrucous leukoplakia, RAS: Recurrent aphthous stomatitis, miRs: Micro RNAs, RT: Reverse transcription, qPCR: Quantitative polymerase chain reaction, AUC: Area under the curve, OLP: Oral lichen planus, SD: Standard deviation

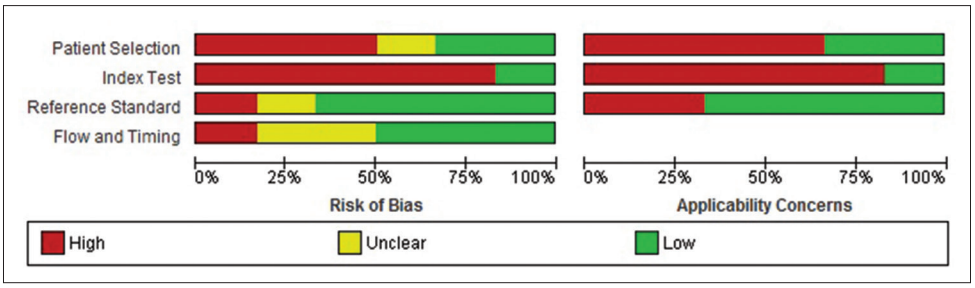

Figure 4: Risk of bias and applicability concerns for the four domains for all six studies

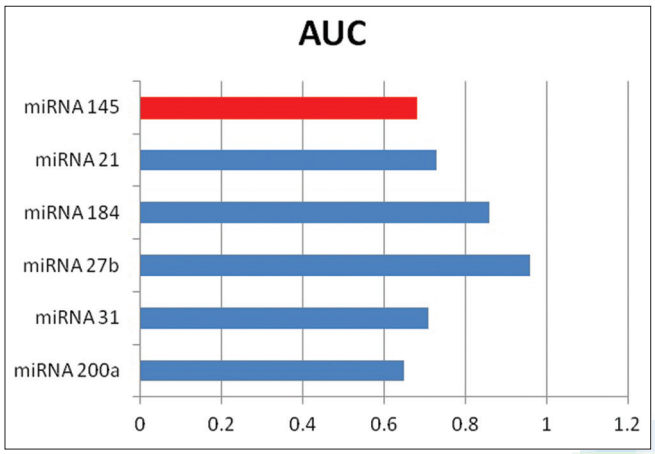

Figure 5: Areas under the curve for the micro RNA considered in 4 studies (Zaharan *et al*., Momen Heravi *et al*., Park *et al*., and Liu *et al*.) for oral squamous cell carcinoma. Red indicates down regulated micro RNA and blue indicates upregulated micro RNA

These 6 studies were done in Caucasian, Asian, African, Taiwanese, Iraqi, and Arabic populations, proving the need for exclusive studies in the Indian populations to assess the diagnostic and prognostic value of miRNA in OPMD [19,26-30].

The AUC curve shows miRNA 27b is the marker of choice in OSCC [26]. However, the Zahran *et al*. study with a low risk of bias had a predetermined cutoff value for the miRNA before the onset of the study. In their study miRNA 184 had the maximum sensitivity and specificity [Figure 5]. They also reported that upregulated miRNA 21 and downregulated miRNA 145 are markers for detecting OPMD with dysplasia, OPMD without dysplasia and OSCC [27].

These findings give insight on the possible use of salivary miRNA as a biomarker in assessing early malignancy in OPMD. Long-term follow-up studies with several population clusters can enhance the reliability of salivary miRNA as a biomarker.

Recommendations for future research

The four studies done in OPMD studied expression of miRNA in cases of leukoplakia, lichen planus, OPMD with dysplasia, and OPMD without dysplasia, but cases of oral submucous fibrosis were not mentioned in any of the studies [26-29]. There is need for studies in oral submucous fibrosis and for more studies comparing salivary miRNA with tissue and serum miRNA. Studies in the Indian population are needed to understand specific genetic variations when evaluating saliva as a surrogate marker in detecting early malignancy. Studies with longer follow-up of saliva samples after the treatment for OPMD and OSCC could enhance the prognostic value of salivary miRNA.

Conclusion

In this systematic review, considering the results of low risk of bias diagnostic study as determined by the quality assessment tool, the upregulated salivary miRNA 184, and miRNA 21 and downregulated salivary miRNA 145 can be used as potential biomarkers to predict malignancy. Of these three, salivary miRNA 184 had highest sensitivity and specificity with an AUC of 0.86 in detecting early malignancy. However, the overall quality of evidence is low in the available literature. There is need for more studies to prove the diagnostic and prognostic potential of salivary miRNA, especially in countries like India where there is an increased prevalence of OPMD.

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Nil.

Conflict of Interest

There are no conflict of interest.

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