REVIEW ARTICLE

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Exploring the role of angiogenesis in fibrosis and malignant transformation in oral submucous fibrosis: a systematic review and meta-analysis

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Abstract (J Korean Assoc Oral Maxillofac Surg 2024;50:243-252)

Angiogenesis is a crucial molecular driver of fibrosis in various inflammatory lesions. Oral submucous fibrosis (OSMF) is a chronic inflammatory fibrotic disorder with malignant potential. The angiogenetic pathways in OSMF remain obscure due to limited research, necessitating an in-depth review. This review aimed to illuminate the cryptic pathogenetic mechanisms of angiogenesis in the disease progression/fibrosis of OSMF and its malignant transformation, providing insights for improved treatment. Extensive literature searches were conducted across an array of databases until October 2023. Original research articles on angiogenesis in OSMF were included, and the risk of bias was assessed using the modified Newcastle–Ottawa scale. RevMan ver. 5.4 (Cochrane Collaboration) was used for data analysis. Thirty-four articles were included for qualitative synthesis and seven for quantitative analysis. Findings revealed that angiogenesis was significantly increased in early-stage OSMF but decreased as the disease advanced. It was also associated with the severity of epithelial dysplasia and malignant transformation. A random-effects model confirmed the upregulation of angiogenesis as a significant risk factor in early-stage fibrosis and malignant transformation. The mounting evidence reinforces that angiogenesis plays a crucial role in the progression of early-stage fibrosis of OSMF and its malignant transformation, opening avenues for diagnostic and therapeutic interventions.

Key words: Angiogenesis, Neoplastic cell transformation, Oral submucous fibrosis, Progression of fibrosis

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I. Introduction

Oral submucous fibrosis (OSMF) is a periodically encountered, potentially malignant disorder distinguished by aggregation of inflammatory cell infiltration and intensified submucosal tissue fibrosis leading to epithelial atrophy and subsequent malignant transformation[1,2]. OSMF is marked by a chronic course and irreversible nature[3] and is characterized by multifactorial aetiologies and an ambiguous pathogenesis[4]. There are several phases of OSMF development, including early, intermediate, and advanced, which are primarily distinguished by the degree of fibrosis[5]. Although the early stage of OSMF is the most prevalent, the intermediate and advanced stages are more symptomatic[6]. The malignant transformation rate of OSMF is around 4.2% (95% confidence interval [CI], 2.7%-5.6%)[2].

In a literature search, we encountered various proposed theories about the pathogenesis of OSMF that consider the role of angiogenesis, which has drawn significant attention[2,7,8]. Furthermore, researchers have employed an array of angiogenic markers (CD31, CD34, factor VIII-related antigen, CD105, VEGF, and VEGFRII) to determine vascularity in OSMF tissues. Most studies have observed downregulation of angiogenesis with the progression of fibrosis in OSMF; however, a three-fold increase in angiogenesis in cases of OSMF with malignant transformation has also been observed[9-12]. Meanwhile, a few investigators reported no discernible connection between angiogenesis and OSMF[13,14]. These conflicting results concerning an angiogenetic factor in OSMF restricts the use of therapeutic anti-angiogenic antibodies.

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The presence of a pathogenetic mechanism of angiogenesis in the progression of fibrosis in OSMF and its malignant transformation is uncertain. In addition, the nature of the link between vascularity and OSMF remains a debate. To identify this relationship, the present systematic review and meta-analysis attempted to clarify the multifaceted role of angiogenesis in OSMF and elucidate its therapeutic implications to prevent the progression of fibrosis and its malignant transformation.

II. Materials and Methods

This exploration was catalogued in the International Prospective Register of Systematic Reviews database (CRD42023483345) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses standard[15].

1. Review question

"Is there a relationship between angiogenesis and progression of fibrosis and/or malignant transformation of OSMF?"

2. PICOS

For this study, the PICOS items were as follows:

- Population: Patients with OSMF (with/without dysplasia), OSMF with oral squamous cell carcinoma, or oral squamous cell carcinoma
- Intervention: Hematoxylin and eosin (H&E)/Masson's trichrome/immunohistochemistry (IHC) staining (using angiogenic markers) of tissue sections or real time-quantitative polymerase chain reaction (RT-qPCR) and western blot (WB) analysis of tissues of patients using angiogenic mRNA/proteins as appropriate
- Comparison: Healthy oral mucosa
- Outcome: Qualitative/quantitative/semi-quantitative analysis of angiogenesis in OSMF
- Study type(s): Literature review and meta-analysis

3. Strategy for identification of studies

The electronic literature databases PubMed, Google Scholar, and the Cochrane Library were searched up to October 31, 2023. The search strategy was as follows: [ALL ("microvascular density" OR "angiogenesis" OR "microvessel density" OR "mean vascular density" OR "morphometry" OR "vascular endothelial growth factors" OR "platelet endothelial cell adhesion molecule-1" OR "PECAM 1" OR "CD31" OR "CD34" OR "vascular cell adhesion molecule-1" OR "VCAM-1" OR "CD106" OR "adhesion molecules" OR "vascular adhesion molecules" OR "intercellular adhesion molecule-1" OR "ICAM-1" OR "endoglin" OR "CD105" OR "factor VIII-related antigen" OR "vascularity" OR "neoangiogenesis" OR "VEGF" OR "VEGFRII") AND ALL ("oral submucous fibrosis" OR "precancer" OR "potentially malignant disorders" OR "OSMF with dysplasia" OR "OSMF with malignant transformation") AND ALL ("immunohistochemistry" OR "polymerase chain reaction" OR "Masson's trichrome stain" OR "special stain" OR "western blot" OR "IHC" OR "RT-PCR")]. A grey literature search was also executed in Google Scholar and Google. The references of published articles were also searched for relevant studies. Supplementary Table 1 describes the study selection process.

4. Eligibility criteria

Articles that fulfilled both of the following inclusion criteria were considered:

(1) A full-text, case-control/cross-sectional original investigation (H&E/Masson's trichrome/IHC/Enzyme-Linked Immunosorbent Assay (ELISA)/RT-qPCR/WB) of OSMF published in English.
(2) Qualitative/quantitative/semi-quantitative analysis of angiogenesis in patients with OSMF/OSMF with epithelial dysplasia/OSMF with Oral Squamous Cell Carcinoma (OSCC) compared to a control group.

Conversely, the following were excluded:

(1) Duplicate, repetitive, and unrelated studies
(2) Unpublished articles, withdrawn/retracted studies, reviews, case reports, conference abstracts, commentaries, opinion articles, and letters to the editor
(3) Abstract or partial article
(4) Studies including oral premalignant disorders other than OSMF
(5) Articles with inadequate information about the methodology and/or results of angiogenesis within OSMF/OSMF with dysplasia/OSCC

5. Article screening and eligibility evaluation

Two investigators reviewed the abstracts and titles of all the publications, eliminating those that failed to fulfil the qualifying requirements. Following selection, the chosen articles underwent a full-text eligibility assessment, during

which the reasons for exclusion were documented. In cases of unresolved discordance, a third investigator was involved for consensus.

6. Study selection and data extraction

The first investigator retrieved data, while the second investigator made amendments to verify the legitimacy of the contents. Subsequent data were extracted, including author name(s), publication year, country of origin, total numbers of OSMF cases without dysplasia/with dysplasia/with malignant transformation and control participants, clinical/histological grading of OSMF, markers employed, method of measurement, angiogenesis assessment criteria, outcome, and inferences.

7. Summary measures, data synthesis, and analysis

The primary outcome of the review was the role of angiogenesis in the progression of fibrosis of OSMF and its malignant transformation. All the extracted data parameters were tabulated and processed in Microsoft Excel 2019 (Microsoft). The meta-analysis was performed using Review Manager software (RevMan ver. 5.4; Cochrane Collaboration). Forest plots of each study with 95% CI were presented. Odds ratios were calculated following bivariate fixed/random-effects regression modeling. The heterogeneity between eligible studies was calculated by inconsistency indexes; I^2 >50% was considered to indicate substantial heterogeneity. P<0.05 was considered statistically significant.

8. Quality assessment

Using the modified Newcastle–Ottawa scale (NOS), two investigators autonomously evaluated the risk of bias, with a third investigator involved to resolve any conflicts. Studies with 7-9 stars were considered to be of high quality, studies receiving 5-6 stars were considered to be of medium quality, and studies with <5 stars were categorized as low quality. The results of modified NOS analysis were generated using RevMan ver. 5.4.

III. Results

1. Study selection

Using various syntaxes, 5,933 articles published through October 31, 2023, were found in the scientific databases. After duplicates were eliminated, 2,341 were shortlisted, and additional filtering by reviewing titles and abstracts resulted in a dataset of 36 articles. After examination of the full texts, 34[9-14,16-35,37-44] articles were chosen for inclusion in the qualitative synthesis after excluding two studies in languages other than English. Of these 34 articles, 4 using IHC to compare angiogenesis and progression of fibrosis[10-12,43] and 3 regarding malignant transformation of OSMF[9,25,29] were included for meta-analysis.(Fig. 1)

2. Study characteristics

Supplementary Tables 2, 3 present data regarding country of origin, authors, total numbers of OSMF and control cases, and the clinical characteristics from all 34 studies. Among these, 33 were conducted in India and 1 was carried out in China. An aggregate of 1,596 OSMF cases were investigated, and their relation to angiogenesis was evaluated.

3. Morphometric analysis of vascularity in hematoxylin and eosin findings

Data regarding the H&E morphometric assessment and characterization of vascularity from 9 studies[13,14,16-22] are presented in Supplementary Tables 2, 4. A single study on qualitative analysis by Sirsat and Pindborg[22] revealed extreme dilatation of blood vessels in the early stage and constriction in the advanced stage of OSMF. Five studies[13,14,16,19,21] involved digital morphometry, with three[16,19,21] reporting increased microvessel density (MVD) in very early-grade OSMF and minimal MVD in advanced-grade OSMF. The mean vascular area (MVA), mean vascular percentage area (MVPA), and mean vascular luminal diameter (MVLD) were highest in the early stage of OSMF and lowest in the advanced stage. In contrast to the above findings, Rajendran et al.[13] found the results of digital analysis of MVD to be roughly the same in OSMF and control tissues, whereas MVPA and MVLD showed a significantly increasing trend with disease progression. Another study by Garg and Mehrotra[14] reported that MVA, MVLD, and mean vascular perimeter (MVP) did not show sustained change with increasing disease severity. Intriguingly, Pal et al.[18] noted that the ratio of vasculature was increased significantly in OSMF cases with dysplasia. In conflict, however, Kapoor et al.[20] found no correlation between MVD and epithelial dysplasia. Sarode et al.[17] observed conspicuous, large dilated vascular spaces in the juxta-

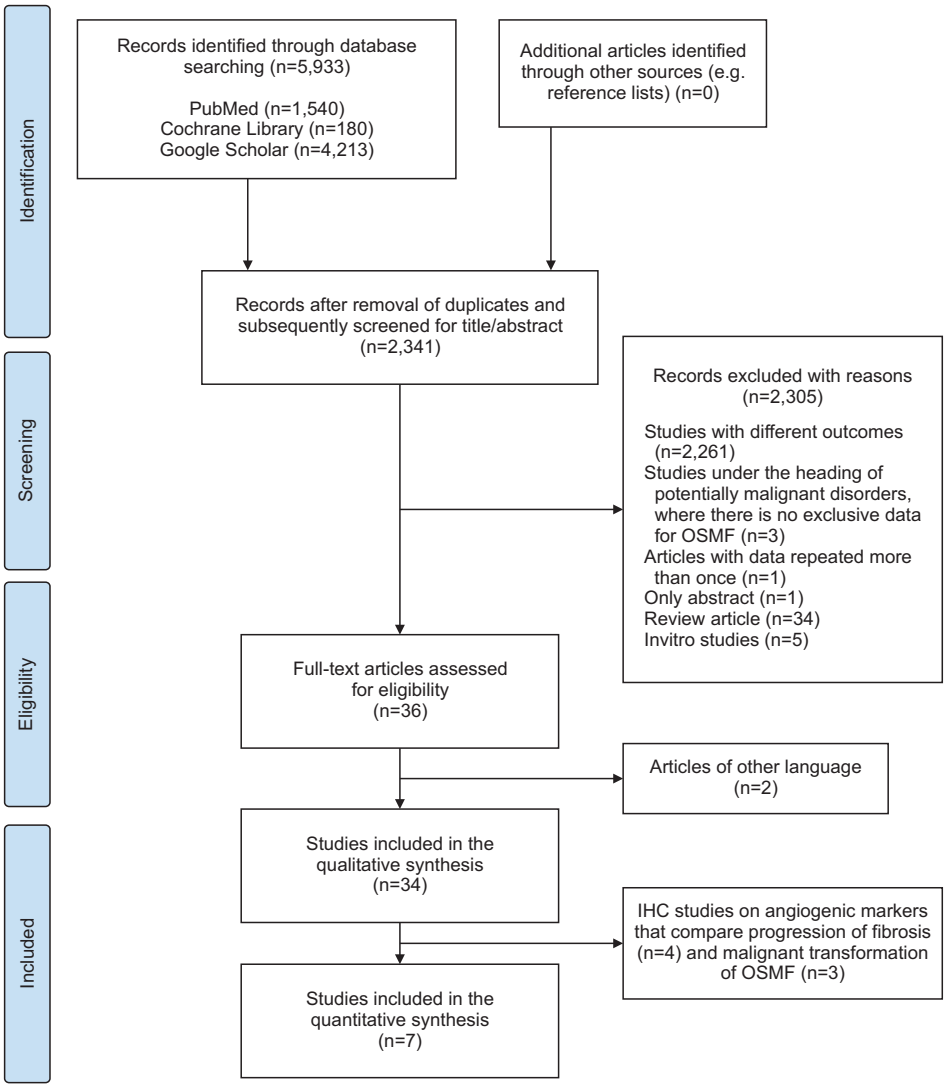

Fig. 1. Flowchart of study selection adapted from the Preferred Reporting Items for Systematic Reviews and Meta-analyses standard. (OSMF: oral submucous fibrosis, IHC: immunohistochemistry)
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epithelial regions of OSMF in patients with OSCC. According to Kapoor et al.[20], there was a non-significant but slightly positive correlation between vascularity and both fibrosis and epithelial thickness.

4. Immunohistochemistry findings of angiogenic markers

Data regarding the IHC findings of angiogenic markers from 22 studies[9-12,24-35,39-44] are presented in Supplementary Tables 4, 5. Nineteen studies[9-12,24-32,35,40-44] used quantitative methods, while two[33,34] and six studies[12,30,31,39,43,44] employed qualitative and semi-quantitative methods, respectively.

1) Factor VIII-related von Willebrand factor (vWf)

Thakkannavar and Naik[10] reported a significant decrease in factor VIII-related vWf MVD with increasing severity of OSMF, contrasting with two other studies[29,42]. Furthermore, Gupta et al.[29] noted a significant increase in factor VIII-related vWf MVD with disease progression of OSMF to malignant transformation.

2) CD31

A single study by Bavle et al.[35] observed a non-significant difference in CD31 MVD with increasing grade of OSMF.

3) CD34

Four studies[11,30,41,43] observed increased CD34 MVD/TVA/MVA in OSMF cases compared to control participants, while two studies[9,12] reported a non-significant difference. Five studies[9,11,12,41,43] mentioned upregulation of CD34 MVD/TVA/MVA in early and moderately advanced OSMF, with a decreasing trend in advanced OSMF. In contrast, Desai et al.[39] found a non-significant difference in CD34 MVD/MVLD/MVAP among grades of OSMF. Another two studies[9,12] found

a significant progressive upregulation of CD34 MVD from OSMF cases without dysplasia to OSMF cases with dysplasia and malignant change.

4) VEGF

According to five[30,33,38,42,43] and one study[32] respectively found VEGF staining intensity/expression[30,33,38,42,43]/VEGF-RII[32] were found to be increased in OSMF compared to control participants. While three studies[12,31,32] reported a non-significant difference in VEGF levels, there were variations in the observed values between OSMF cases and controls. Study 32 noted higher VEGF values in OSMF cases compared to controls, whereas studies 12 and 31 found lower VEGF values in OSMF cases than in controls. Three studies[31,33,42] found decreasing VEGF expression with increasing grade of OSMF, in disagreement with two studies[12,38]. These two studies demonstrated a non-significant difference in VEGF expression among grades of OSMF. Another two studies[31,32] reported significantly increased spatial localization (proliferative/differentiative layers) of VEGF/VEGFRII in the epithelium/submucosa of OSMF cases with dysplasia, and this finding was associated with severity of dysplasia. Madhavan Nirmal et al.[12] observed significant increases in VEGF during progression from OSMF without epithelial dysplasia to OSMF with epithelial dysplasia and micro-invasion.

5) CD105

CD105 staining in normal oral mucosa (NOM) was absent in three[31,32,34] studies, while CD105 expression was assessed in four studies[25-27,41]. Pammar et al.[41] observed decreasing CD105 MVD with increasing grade of OSMF. Three studies[31,32,34] mentioned significantly increased CD105 MVD, thicker vascular diameter, and increased area of extension in OSMF with dysplasia compared to OSMF without dysplasia. Six studies[25-27,31,32,34] have reported that, with increasing grade of OSMF dysplasia, there is a parallel significant upregulation of CD105 MVD or CD105-positive vessels. Gadbail et al.[25] commented that CD105 MVD significantly increased with disease progression from OSMF without dysplasia to OSMF with dysplasia to malignant transformation. Finally, two studies[24,28] found that CD105 MVD was significantly greater in the OSCC group compared to the OSCC with OSMF group.

5. Other methods for assessment of angiogenic markers

Studies using Masson's trichrome stain[23], RT-qPCR[33,37,38], or WB[33] found significantly increased VEGF mRNA expression in OSMF[37,38]. In two studies[23,33], MVD and VEGF mRNA and proteins decreased with disease progression.

6. Quality assessment

Of the 26 case-control studies, we categorized three as high quality and 23 as moderate quality based on the modified NOS evaluation. A moderate-quality designation was given to all eight of the cross-sectional studies. Not a single involved study was of poor quality. Supplementary Fig. 1 presents the quality designations of the studies.

7. Meta−analysis

Random-effects and fixed-effects models confirmed that significantly increased angiogenesis was associated with early-stage fibrosis of OSMF[11,12,43] (combined mean difference, 7.29; 95% CI, 2.08-12.49, P=0.006 with substantial heterogeneity) or malignant transformation of OSMF[9,25,29] (combined mean difference, 259.73; 95% CI=24.70-2731.71; P=0.04 with null heterogeneity).(Supplementary Fig. 2, 3) Meanwhile, significantly decreased angiogenesis exhibited an association with the advanced-stage fibrosis of OSMF[10-12,43] (random-effects model: combined mean difference, −8.74; 95% CI, −17.17 to −0.31; P=0.04 with substantial heterogeneity).(Supplementary Fig. 4)

IV. Discussion

In addition to being a disorder of the connective tissue, OSMF might transform into malignancy[45,46]. Recently, evidence has emerged to substantiate the critical role of angiogenesis in fibrotic disorders[47,48]. Thus, the present systematic review and meta-analysis was conducted for in-depth understanding of the angiogenic mechanism in the progression of OSMF and its malignant transformation to aid practitioners in treatment. Furthermore, endeavors were undertaken to clarify the role of angiogenesis in the progression of fibrosis of OSMF and its malignant transformation.(Fig. 2) The present review encompassed 34 original studies involving the methodology and assessment of vascularity and neo-angiogenesis and their potential roles in OSMF.

Most morphometry studies reported increased MVD in

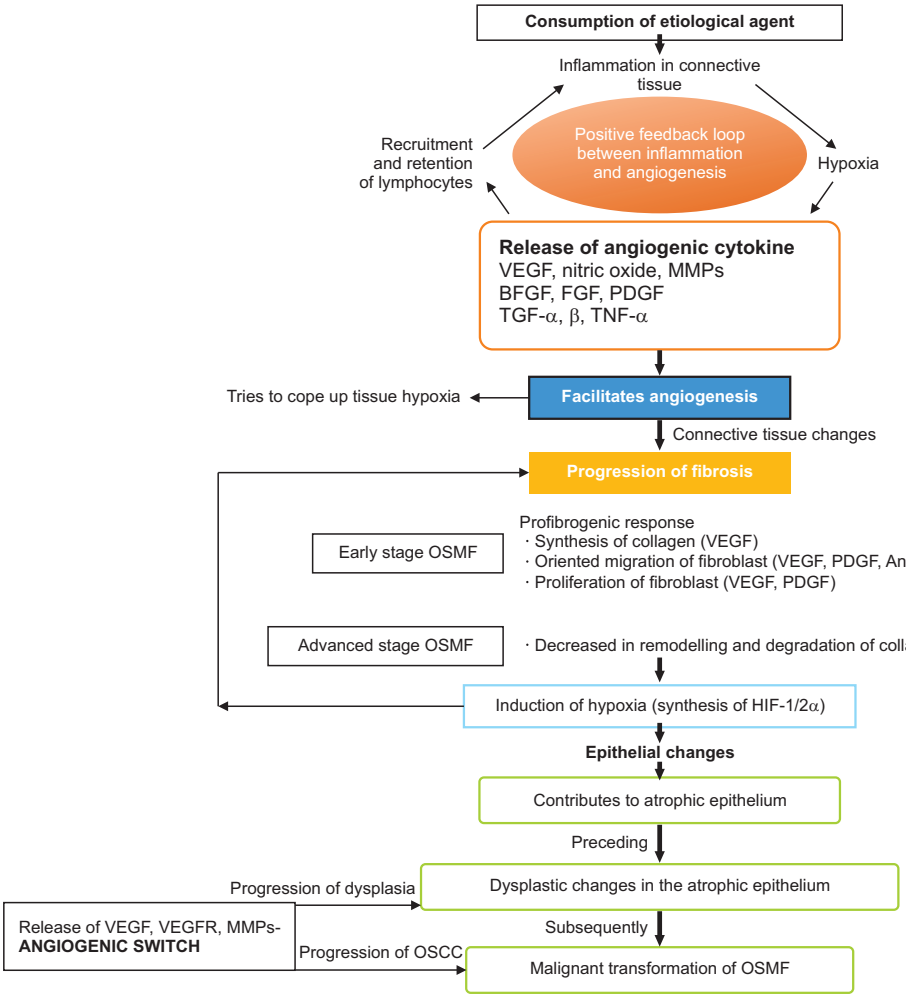

Fig. 2. Flowchart of the pathogenetic mechanism of angiogenesis in the progression of fibrosis in OSMF and its malignant transformation. (BFGF: basic fibroblast growth factor, OSMF: oral submucous fibrosis, PDGF: platelet derived growth factor, OSCC: oral squamous cell carcinoma)
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the very early stage of OSMF, while greater MVA, MVPA, and MVLD were observed in the early stage of OSMF with maximum dilatation. In contrast, later advanced stages of OSMF are marked by reduced MVD, MVA, and MVPA with constriction or near obliteration of the blood vessel lumen[16,19,21-23]. Notably, two studies[13,14] disagree with these findings. The dissimilar results could be attributed to a small sample size or ambiguities in methodology. Moreover, dilated vascular blood vessels in the moderately advanced and advanced stages of OSMF are considered indicators of tissue hypoxia[13,22]. When predominantly located in juxta-epithelial areas, such vessels are an indicator of the potential malignancy of OSMF[17]. In relating vascularity and epithelial dysplasia, one study each witnessed a significant or non-significant association of TVA[18] or MVD[20] with OSMF cases showing dysplasia, respectively. The contradictory finding reported by Kapoor et al.[20] might be attributable to assessment of epithelial dysplasia in OSMF (atrophic epithelium) using the World Health Organization (WHO) three-tier classification. The issue with using the WHO's three-tier classification to assess epithelial dysplasia in OSMF, particularly in atrophic epithelium, lies in its potential limitations. The WHO classification may not fully capture the nuances of dysplasia in the specific context of OSMF, as it was developed for general epithelial abnormalities and may overlook subtleties unique to atrophic epithelium. Other classification systems, such as binary grading (low vs. high), might offer a more tailored approach, potentially providing a clearer assessment of progression risk in OSMF cases. Kapoor et al.[20] also observed a non-significant but slightly positive correlation between vascularity and both fibrosis and epithelial thickness.

A total of 22 studies analysed IHC results of angiogenic markers, including factor VIII-related vWf, CD31, CD34, VEGF, and CD105. Factor VIII-related vWf MVD was significantly decreased with increasing severity of OSMF in one study[10] but was not decreased in two studies[29,42]. This disparity is related to the uneven allocation or absence of other disease stages of OSMF and the employment of Gupta et al.[29]

empoyed Khanna and Andrade's[36]. In addition, Gupta et al.[29] observed increased vascularity as the disease progressed from moderately advanced to advanced OSMF or OSMF with malignant transformation.

Expression of CD31 MVD was non-significantly associated with different grades of OSMF[35]. This conflicting result may have resulted from the unequal distribution of OSMF grades and the use of Bavle et al.[35] empoyed Khanna and Andrade's 1995 OSMF grading criteria[36].

Four studies[11,30,41,43] reported that CD34 MVD was significantly increased in OSMF cases compared to the control group. In comparison, two studies[9,12] observed an upsurge of CD34 MVD in NOM. This difference could have arisen from subclinical inflammation or a local reaction to an anesthetic solution in NOM. In comparing various grades of OSMF, five studies[9,11,12,41,43] showed a decreasing trend of CD34 MVD as OSMF advanced, in conflict with Desai et al.[39] found a non-significant difference in CD34 MVD/MVLD/MVAP among grades of OSMF. This difference in variation might be attributed to methodological differences and an uneven distribution of grades of OSMF cases. Concerning the nature of the epithelium, two studies[9,12] detected a significant increase in CD34 MVD from OSMF with no dysplasia to OSMF with dysplasia and to OSMF with malignant transformation.

Considering VEGF immunoreactivity, five studies[30,32,33,39,44] documented increased expression of VEGF or VEGFRII in OSMF. Two studies each demonstrated a significant[31,33] and non-significant[12,39] difference in VEGF expression among grades of OSMF. There was significantly increased VEGF or VEGFRII expression/spatial localization in OSMF cases with dysplasia, and this trend was related to severity of epithelial dysplasia[31,32]. OSMF cases with moderate or severe dysplasia displayed spatial localization of VEGF in submucosa[31,32], and significant increases in VEGF were recorded in the transition from OSMF without epithelial dysplasia to OSMF with epithelial dysplasia and micro-invasion[12]. The above-mentioned findings confirmed that transmission of VEGF from dysplastic epithelium to the submucosa is essential for neoangiogenesis in the submucosa[32].

CD105 is a novel marker for neo-angiogenesis, and the assessment of MVD using CD105 revealed a reduction in expression with increasing grade of OSMF[41]. The MVD of CD105, area of extension, maturation of blood vessels, and presence of blood vessels proximal to the basement membrane were significantly increased in OSMF with dysplasia and correlated with severity of epithelial dysplasia[25-27,31,32,34]. Gadbail et al.[25] found that MVD was significantly increased in the progression from OSMF without dysplasia to OSMF with dysplasia and OSMF with malignant transformation. Collectively, these findings suggest a role of neoangiogenesis in the progression of fibrosis and malignant transformation of OSMF. Two studies[24,28] have attempted to demonstrate the biological distinction of OSMF with OSCC and OSCC alone. Elsewhere, CD105 MVD was found to be significantly greater in the OSCC group compared to the OSCC with OSMF group. Owing to the paucity of data, however, future studies need to validate this finding.

In corroborating the VEGF IHC findings, RT-qPCR and WB analysis revealed increased VEGF-A mRNA expression in OSMF[37,38]. Regarding grades of OSMF, early-stage disease correlated with significantly greater VEGF-A mRNA expression and VEGF protein concentration, which decreased as the disease progressed[33].

To summarize, MVD, TVA, MVA, MVLD, and MVAP (H&E/CD31/CD34/factor VIII-related vWf/CD105 neoangiogenesis) and VEGF immunoreactivity, proteins, and mRNA expression are significantly upregulated in very early and early stages of OSMF and progressively decrease with increasing severity. Furthermore, angiogenesis is also associated with increased severity of epithelial dysplasia in OSMF and a three-fold increase in vascularity or neo-angiogenesis in OSMF with malignant transformation. This confirms the angiogenic switch in the atrophic epithelium of OSMF preceding OSMF with epithelial dysplasia and subsequent transformation to malignancy.(Supplementary Fig. 5) Thus, angiogenesis does play a pivotal role in the progression of fibrosis in early-stage OSMF and in malignant transformation, rendering it a possible marker of disease activity in OSMF. Moreover, the choice of an angiogenic marker—especially VEGF and CD105—might be a useful diagnostic and prognostic marker for discriminating disease stages of OSMF as well as OSMF cases with/without epithelial dysplasia and malignant transformation.

Our forest plot results also indicated that the risk for early-stage fibrosis of OSMF and malignant transformation of OSMF is significantly greater in cases with increased angiogenesis; advanced-stage fibrosis of OSMF correlated with decreased angiogenesis.

V. Conclusion

This systematic review and meta-analysis demonstrated that progression of fibrosis in the early stage of OSMF and its

malignant transformation are primarily mediated by angiogenesis. Also, in the advanced stage of OSMF, progression of fibrosis is principally attributed to failure of collagen degradation or remodeling. In addition, our work emphasizes that neoangiogenesis might be an appropriate target to resolve early-stage fibrosis and malignant transformation in OSMF, which could alleviate this fibrotic disease. Randomized clinical trials on angiogenic inhibitors are suggested to ascertain their therapeutic implications.

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Authors' Contributions

K.R. participated in methodology, resources, data curation, formal analysis, writing original draft. A.C. participated in conceptualization, data curation, project administration, resources, supervision, validation, writing review & editing of manuscript. D.R. participated in data curation, formal analysis, validation, writing original draft. M.K. participated in conceptualization, project administration, resources, supervision, validation, writing review & editing of the manuscript. R.A. participated in data curation, conceptualization, project administration, resources, supervision, validation, writing review & editing of manuscript. All authors read and approved the final manuscript.

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Supplementary Materials

Supplementary data is available at http://www.jkaoms.org.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Rajendran R. Oral submucous fibrosis: etiology, pathogenesis, and future research. Bull World Health Organ 1994;72:985-96.
2. Ekanayaka RP, Tilakaratne WM. Oral submucous fibrosis: review on mechanisms of malignant transformation. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:192-9. https://doi.org/10.1016/j.oooo.2015.12.018
3. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol 1966;22:764-79. https://doi.org/10.1016/0030-4220(66)90367-7
4. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: review on aetiology and pathogenesis. Oral Oncol 2006;42:561-8. https://doi.org/10.1016/j.oraloncology.2005.08.005
5. More CB, Gupta S, Joshi J, Verma SN. Classification system for oral submucous fibrosis. J Indian Acad Oral Med Radiol 2012;24:24-9. https://doi.org/10.5005/jp-journals-10011-1254
6. Haider SM, Merchant AT, Fikree FF, Rahbar MH. Clinical and functional staging of oral submucous fibrosis. Br J Oral Maxillofac Surg 2000;38:12-5. https://doi.org/10.1054/bjom.1999.0062
7. Arakeri G, Rai KK, Hunasgi S, Merkx MAW, Gao S, Brennan PA. Oral submucous fibrosis: an update on current theories of pathogenesis. J Oral Pathol Med 2017;46:406-12. https://doi.org/10.1111/jop.12581
8. Ray JG, Ranganathan K, Chattopadhyay A. Malignant transformation of oral submucous fibrosis: overview of histopathological aspects. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:200-9. https://doi.org/10.1016/j.oooo.2015.11.024
9. Pandiar D, Shameena P. Immunohistochemical expression of CD34 and basic fibroblast growth factor (bFGF) in oral submucous fibrosis. J Oral Maxillofac Pathol 2014;18:155-61. https://doi.org/10.4103/0973-029X.140718
10. Thakkannavar SS, Naik VV. Histochemical and immunohistochemical analysis of collagen fibers and microvascular density in various grades of oral submucous fibrosis. Iran J Pathol 2019;14:127-34. https://doi.org/10.30699/IJP.14.2.127
11. Tekade SA, Chaudhary MS, Tekade SS, Sarode SC, Wanjari SP, Gadbail AR, et al. Early stage oral submucous fibrosis is characterized by increased vascularity as opposed to advanced stages. J Clin Diagn Res 2017;11:ZC92-6. https://doi.org/10.7860/JCDR/2017/25800.9948
12. Madhavan Nirmal R, Veeravarmal V, Bhavani S, Srinivasan P, Austin RD. Evaluation of micro-vessel density (Mvd) and vascular endothelial growth factor (Vegf) as possible indicator of malignant transformation in oral submucous fibrosis. J Dent Med Sci 2016;15:72-7.
13. Rajendran R, Paul S, Mathews PP, Raghul J, Mohanty M. Characterisation and quantification of mucosal vasculature in oral submucous fibrosis. Indian J Dent Res 2005;16:83-91.
14. Garg N, Mehrotra RR. Morphometric analysis of epithelial thickness and blood vessels in different grades of oral submucous fibrosis. Malays J Pathol 2014;36:189-93.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097. https://doi.org/10.1371/journal.pmed.1000097
16. Singh M, Chaudhary AK, Pandya S, Debnath S, Singh M, Singh PA, et al. Morphometric analysis in potentially malignant head and neck lesions: oral submucous fibrosis. Asian Pac J Cancer Prev 2010;11:257-60.
17. Sarode SC, Sarode GS, Sengupta N, Ghone U, Patil S. Conspicuous and frank dilated vascular spaces: a marker of malignant transformation in oral submucous fibrosis. J Oral Biol Craniofac Res 2021;11:365-7. https://doi.org/10.1016/j.jobcr.2021.03.007

18. Pal M, Nawn D, Lahiri P, Das D, Paul RR, Chakraborty D. Malignant potentiality assessment of oral submucous fibrosis through semi-quantitative approach. J Oral Maxillofac Pathol 2020;24:188. https://doi.org/10.4103/jomfp.JOMFP_297_19
19. Debnath S, Mitra B, Paul B, Saha TN, Maity A. Morphometric analysis of oral submucous fibrosis and its correlation with histological staging and clinical severity of trismus. Egypt J Ear Nose Throat Allied Sci 2013;14:85-90. https://doi.org/10.1016/j.ejenta.2013.04.005
20. Kapoor R, Sansare K, Tamgadge S, Karjodkar F, Mehra A, Mishra I, et al. Epithelial atrophy, fibrosis and vascularity correlation with epithelial dysplasia in oral submucous fibrosis, a prospective study. J Microsc Ultrastruct 2020;10:1-6. https://doi.org/10.4103/JMAU.JMAU_36_20
21. Murgod VV, Kale AD, Angadi PV, Hallikerimath S. Morphometric analysis of the mucosal vasculature in oral submucous fibrosis and its comparison with oral squamous cell carcinoma. J Oral Sci 2014;56:173-8. https://doi.org/10.2334/josnusd.56.173
22. Sirsat SM, Pindborg JJ. The vascular response in early and advanced oral submucous fibrosis. Acta Pathol Microbiol Scand 1967;70:179-84. https://doi.org/10.1111/j.1699-0463.1967.tb01280.x
23. Gupta S, Sharma M, Banerjee S, Holikatti K, Kamble P, Goyal JV. The immunolocalization of mast cells in the pathology of oral submucous fibrosis. Cureus 2023;15:e40069. https://doi.org/10.7759/cureus.40069
24. Hande AH, Chaudhary MS, Gadbail AR, Gawande MN, Patil SK, Zade PR, et al. Significance of HIF-1α and CD105 in establishing oral squamous cell carcinoma associated with oral submucous fibrosis a distinct clinicopathological entity. J Cancer Res Ther 2022;18:33-41. https://doi.org/10.4103/jcrt.JCRT_591_20
25. Gadbail AR, Chaudhary MS, Sarode SC, Gondivkar SM, Belekar L, Mankar-Gadbail MP, et al. Ki67, CD105 and α-smooth muscle actin expression in disease progression model of oral submucous fibrosis. J Investig Clin Dent 2019;10:e12443. https://doi.org/10.1111/jicd.12443
26. Gadbail AR, Chaudhary MS, Sarode SC, Gawande M, Korde S, Tekade SA, et al. Ki67, CD105, and α-SMA expressions better relate the binary oral epithelial dysplasia grading system of World Health Organization. J Oral Pathol Med 2017;46:921-7. https://doi.org/10.1111/jop.12612
27. Gadbail AR, Chaudhary M, Sarode SC, Gondivkar S, Tekade SA, Zade P, et al. Ki67, CD105, and α-SMA expression supports the transformation relevant dysplastic features in the atrophic epithelium of oral submucous fibrosis. PLoS One 2018;13:e0200171. https://doi.org/10.1371/journal.pone.0200171
28. Gadbail AR, Korde S, Chaudhary MS, Sarode SC, Gondivkar SM, Dande R, et al. Ki67, CD105, and α-SMA expression supports biological distinctness of oral squamous cell carcinoma arising in the background of oral submucous fibrosis. Asian Pac J Cancer Prev 2020;21:2067-74. https://doi.org/10.31557/APJCP.2020.21.7.2067
29. Gupta S, Shetty DC, Gulati N, Juneja S, Jain A. Potentiated action on the progression of OSMF by hypoxia mediated signaling pathway by the epithelial mesenchymal transition and angiogenic apparatus. J Cancer Res Ther 2023;19(Suppl 1):S389-96. https://doi.org/10.4103/jcrt.jcrt_502_21
30. Sheelam S, Reddy SP, Kulkarni PG, Nandan S, Keerthi M, Raj GS. Role of cell proliferation and vascularity in malignant transformation of potentially malignant disorders. J Oral Maxillofac Pathol 2018;22:281. https://doi.org/10.4103/jomfp.JOMFP_182_17
31. Anura A, Das RK, Pal M, Paul RR, Ray AK, Chatterjee J. Correlated analysis of semi-quantitative immunohistochemical features of E-cadherin, VEGF and CD105 in assessing malignant potentiality of oral submucous fibrosis. Pathol Res Pract 2014;210:1054-63. https://doi.org/10.1016/j.prp.2014.06.009
32. Anura A, Conjeti S, Das RK, Pal M, Paul RR, Bag S, et al. Computer-aided molecular pathology interpretation in exploring prospective markers for oral submucous fibrosis progression. Head Neck 2016;38:653-69. https://doi.org/10.1002/hed.23962
33. Lin Y, Jiang Y, Xian H, Cai X, Wang T. Expression and correlation of the Pi3k/Akt pathway and VEGF in oral submucous fibrosis. Cell Prolif 2023;56:e13491. https://doi.org/10.1111/cpr.13491
34. Das RK, Pal M, Barui A, Paul RR, Chakraborty C, Ray AK, et al. Assessment of malignant potential of oral submucous fibrosis through evaluation of p63, E-cadherin and CD105 expression. J Clin Pathol 2010;63:894-9. https://doi.org/10.1136/jcp.2010.078964
35. Bavle RM, Paremala K, Sowmya M, Sudhakara M, Reshma V, Hosthor S. Predicting the malignant transformation of oral submucous fibrosis using quantitative biomarkers p63 and CD31. J Orofac Sci 2020;12:52-60. https://doi.org/10.4103/jofs.jofs_6_20
36. Khanna JN, Andrade NN. Oral submucous fibrosis: a new concept in surgical management. Report of 100 cases. Int J Oral Maxillofac Surg 1995;24:433-9. https://doi.org/10.1016/s0901-5027(05)80473-4
37. Nayak S, Goel MM, Bhatia V, Chandra S, Makker A, Kumar S, et al. Molecular and phenotypic expression of decorin as modulator of angiogenesis in human potentially malignant oral lesions and oral squamous cell carcinomas. Indian J Pathol Microbiol 2013;56:204-10. https://doi.org/10.4103/0377-4929.120366
38. Nayak S, Goel MM, Chandra S, Bhatia V, Mehrotra D, Kumar S, et al. VEGF-A immunohistochemical and mRNA expression in tissues and its serum levels in potentially malignant oral lesions and oral squamous cell carcinomas. Oral Oncol 2012;48:233-9. https://doi.org/10.1016/j.oraloncology.2011.10.003
39. Desai RS, Mamatha GS, Khatri MJ, Shetty SJ. Immunohistochemical expression of vascular endothelial growth factor (VEGF) and its possible role in tumour progression during malignant transformation of atrophic epithelium in oral submucous fibrosis. Curr Angiogenes 2012;1:347-53. https://doi.org/10.2174/2211552811201040347
40. Desai RS, Mamatha GS, Khatri MJ, Shetty SJ. Immunohistochemical expression of CD34 for characterization and quantification of mucosal vasculature and its probable role in malignant transformation of atrophic epithelium in oral submucous fibrosis. Oral Oncol 2010;46:553-8. https://doi.org/10.1016/j.oraloncology.2010.04.004
41. Pammar C, Nayak RS, Kotrashetti VS, Hosmani J. Comparison of microvessel density using CD34 and CD105 in oral submucous fibrosis and its correlation with clinicopathological features: an immunohistochemical study. J Cancer Res Ther 2018;14:983-8. https://doi.org/10.4103/0973-1482.181186
42. Sabarinath B, Sriram G, Saraswathi TR, Sivapathasundharam B. Immunohistochemical evaluation of mast cells and vascular endothelial proliferation in oral submucous fibrosis. Indian J Dent Res 2011;22:116-21. https://doi.org/10.4103/0970-9290.80009
43. Sharma E, Tyagi N, Gupta V, Narwal A, Vij H, Lakhnotra D. Role of angiogenesis in oral submucous fibrosis using vascular endothelial growth factor and CD34: an immunohistochemical study. Indian J Dent Res 2019;30:755-62. https://doi.org/10.4103/ijdr.IJDR_186_17
44. Sharada P, Swaminathan U, Nagamalini BR, Kumar KV, Ashwini BK, Lavanya V. Coalition of E-cadherin and vascular endothelial growth factor expression in predicting malignant transformation in common oral potentially malignant disorders. J Oral Maxillofac Pathol 2018;22:40-7. https://doi.org/10.4103/jomfp.JOMFP_13_18
45. Kaur A, Rustagi N, Ganesan A, Pm N, Kumar P, Chaudhry K. Minimal clinically important difference of mouth opening in oral submucous fibrosis patients: a retrospective study. J Korean Assoc Oral Maxillofac Surg 2022;48:167-73. https://doi.org/10.5125/jkaoms.2022.48.3.167
46. Qayyum MU, Janjua OS, Ul Haq E, Zahra R. Nasolabial and extended nasolabial flaps for reconstruction in oral submucous fibrosis. J Korean Assoc Oral Maxillofac Surg 2018;44:191-7. https://doi.org/10.5125/jkaoms.2018.44.4.191

47. Bocca C, Novo E, Miglietta A, Parola M. Angiogenesis and fibrogenesis in chronic liver diseases. Cell Mol Gastroenterol Hepatol 2015;1:477-88. https://doi.org/10.1016/j.jcmgh.2015.06.011
48. Elpek GÖ. Angiogenesis and liver fibrosis. World J Hepatol 2015;7:377-91. https://doi.org/10.4254/wjh.v7.i3.377

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