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Review Paper

A Review on Screening Model for Submucosa Fibrosis

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ABSTRACT

Oral submucous fibrosis (OSF) is characterized by abnormal collagen deposition. It is a precancerous disorder and transforms into a malignant tumor in 1.5–15% of all cases. Symptoms include submucous fibrosis, ulceration, xerostomia, a burning sensation, and restricted mouth opening. All of these greatly interfere with patient quality of life. The present review introduces OSF from a molecular perspective and summarizes what is known about its underlying mechanisms, and therapeutic interventions. In addition to the aggressive treatment of OSF, its prevention is also important. Oral submucous fibrosis (OSF) is a collagen deposition disorder that affects a patient's oral function and quality of life. It may also potentially transform into malignancy. This review summarizes the risk factors, pathogenic mechanisms, and treatments of OSF based on clinical and bio-molecular evidence. Betel nut chewing is a major risk factor that causes OSF in Asia. However, no direct evidence of arecoline-induced carcinogenesis has been found in animal models. Despite identification of numerous biomarkers of OSF lesions and conducting trials with different drug combinations, clinicians still adopt conservative treatments that primarily focus on relieving the symptoms of OSF. Treatments focus on reducing inflammation and improving mouth opening to improve a patient's quality of life. In conclusion, high-quality clinical studies are needed to aid clinicians in developing and applying molecular biomarkers as well as standard treatment guidelines.

INTRODUCTION

Submucosal fibrosis refers to the thickening and scarring of the submucosal layer of tissue, typically due to chronic inflammation or injury. This condition can occur in various organs, including the esophagus (as in eosinophilic esophagitis), the colon (in conditions like inflammatory bowel disease), or the lungs (in the case of conditions like pulmonary fibrosis). It often results in impaired function and can complicate treatment options. Screening models for submucosal fibrosis help in early detection,

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diagnosis, and management of this condition. Oral submucous fibrosis (OSF) is a high risk precancerous condition which was first described in the early 1950s characterized by changes in the connective tissue fibers of the lamina propria and deeper parts leading to stiffness of the mucosa and restricted mouth opening seen predominantly in people of Asian descent. The disease is predominantly seen in India, Bangladesh, Sri Lanka, Pakistan, Taiwan, China and among other Asiatics, with a reported prevalence ranging up to 0.4% in Indian rural population (Murti et al., 1995). Epidemiological and in vitro experimental studies have shown that chewing areca nut (Areca catechu) is the major aetiological factor for OSF (Caniff and Harvey, 1981). Although there are regional variations in the type of areca nut products used in India, the betel quid (BQ) was the most popular and prevalent habit in ancient Indian culture. But in 1980, both areca quid products such as Pan masala (Areca quid) and Gutkha (AQ tobacco) were introduced in Indian market as commercial preparations. Oral submucous fibrosis (OSF) is a chronic disease that produces scars, tissue fibrosis, and precancerous lesions. It frequently occurs in the buccal mucosa [1,2]. Pathological characteristics include chronic inflammation, excessive collagen deposition in the connective tissues below the oral mucosal epithelium, local inflammation in the lamina propria or deep connective tissues, and degenerative changes in the muscles. OSF patients experience a severe burning sensation in the mouth after ingesting spicy foods. Other symptoms of OSF include dry mouth, pain, taste disorders, restricted tongue mobility, trismus, dysphagia, and altered tone. This disease contributes significantly to mortality because of its high malignant transformation rate (1.5–15%) [3]. The incidence of OSF differs with ethnicity and region and is closely associated with diet, habits, and culture [4,5,6]. India has the greatest number of OSF patients worldwide but the disease also occurs in Taiwan and other Asian countries [7,8]. There are also numerous OSF patients in South Africa as this country has many Indian immigrants. According to World Health Organization (WHO) statistics, there are >5 million OSF patients globally [9,10]. In India, OSF occurs more often in women than men but the opposite is true for other regions. The patient age range is 20–40 y. Causative factors of OSF include autoimmunity, vitamin B, C, and iron deficiencies, chewing betel nut, consumption of spicy foods, human papilloma virus (HPV) infection, and genetic mutations [11,12,13,14,15]. Epidemiological studies have shown that chewing betel nut is one of the most significant risk factors for OSF [16]. Among OSF patients in China, 62.3% have the habit of chewing betel nuts [17]. Certain studies also reported that habits such as chewing and smoking tobacco and drinking alcohol increase the risk of OSF [12,18]. A study in Taiwan indicated that a high proportion of betel quid chewers are also tobacco smokers (86%) or alcohol drinkers (74%) [19]. Chewing betel nut and tobacco together substantially increases the incidence of OSF [20]. Other studies confirmed that drinking alcohol and chewing betel nut have an additive effect on OSF induction [19,21]. OSF is widely recognized as a precursor to oral precancer. Previous studies found that OSF patients in China have a 1.19% chance of developing oral cancer. In India, ~7.6% of all OSF patients develop oral cancer [8,22]. Previous studies proved that the duration of OSF and the extent to which its symptoms worsen are directly correlated with oral cancer progression. OSF generally progresses to oral cancer 3–16 y after the initial OSF diagnosis. Unfortunately, there are no effective treatments for OSF available for clinical use. Here, the aim of this work is review the existing literature on the pathogenesis, molecular diagnosis, and clinical treatment of OSF in order

to elucidate effective molecular prevention, diagnosis, and treatment strategies for it.

Pathogenesis

The role of the constituents of areca nut in the pathogenesis of OSF has been studied in detail over last two decades. It is apparent that fibrosis and hyalinization of subepthelial tissues account for most of the clinical features encountered in this condition. Moreover, substantial amount of research on elucidating the etiology and pathogenesis appear to have been focused on changes in the extracellular matrix (ECM). It is logical to hypothesize that the increased collagen synthesis or reduced collagen degradation as possible mechanisms in the development of the disease. There are numerous biological pathways involved in the above processes and, it is likely that the normal regulatory mechanisms are either down regulated or up regulated at different stages of the disease

Epidemiology of OSF

Oral submucous fibrosis (OSF) is a common oral precancerous lesion in Asian countries, especially in areas with a culture of chewing betel nuts. OSF is caused by abnormal collagen deposition in the connective tissues and affect mouth functions. Although there is no immediate danger with a diagnosis of OSF, it seriously affects the quality of life of patients. OSF interferes with a patient's quality of life because of annoying symptoms, such as ulceration, xerostomia, a burning sensation, and limitation in mouth opening. Moreover, OSF is a pre-malignant disorder with the potential for malignant transformation. Therefore, it is necessary to understand its clinical features, prevalence, malignant transformation rate, and risk factors. In Asia, the major risk factor for OSF is betel nut chewing. To reduce the occurrence of OSF, it is important to discover the pre-malignant disorder in the early stage, and understand the pathologic mechanism and treatment options. This review introduces OSF from both clinical and molecular perspectives and focuses on the epidemiology, diagnostic biomarkers, mechanisms of OSF induction and transformation, and aggressive therapeutic interventions.

Clinical Features of OSF

The oral mucosa can be divided into masticatory, specialized, and lining mucosa based on their function and histology. OSF occurs on all three types of mucosae, and most frequently occurs in the buccal mucosa [1,2], retromolar area, and the soft palate sites. The symptoms of OSF include dry mouth, pain, taste disorders, restricted tongue mobility, trismus, dysphagia, and changed tone movability. In addition to the oral cavity, the fibrosis even involves the pharynx and esophagus. In OSF cases, the soft and pink oral mucosa initially becomes inelastic and slightly blanched. Subsequently, the mucosa becomes markedly inelastic and opaque, with white blanching, and appears papery white and tough on palpation, with a firm vertical band, which can be felt just opposite the premolar region. In the later stages, the lips and palate are also involved with lesions occurring on one or more sites. Patients with OSF experience a severe burning sensation in their mouths after ingesting spicy food. Finally, the patients' abilities to open their mouths become limited and their oral mucosae become hardened; moreover, they have poor wound healing, and their cheeks and lips become tightly held against their teeth.

Prevalence of OSF

OSF is a chronic oral disease that produces scar and tissue fibrosis. It is a pre-malignant disorder that may eventually lead to oral cancer. This disease contributes significantly to mortality

because of its high malignant transformation rate (1.5–15%) [3]. OSF occurrence differs with ethnicity and region and is closely associated with diet, habits, and culture [4,5,6]. South and South-East Asia have the highest prevalence of OSF patients [5,7,8]. Additionally, South Africa also has a high prevalence of OSF patients because of a large proportion of Indian immigrants. The prevalence of OSF varies among South-East Asian countries. The prevalence is reported to be 0.9–4.7% in China [9], 0.62–6.42% in India, 0.15–14.6% in Vietnam [10], and 0.086–17.6% in Taiwan [11]. Based on the World Health Organization statistics, there are more than 5 million OSF patients globally [12,13]. The ages of OSF patients range from 8 to 80 years [14], with varying mean age across different studies.

The Malignant Transformation Rate of OSF

OSF is widely recognized as condition precancerous to oral cancer. The malignant transformation rate of OSF ranges from 1.2 to 23% worldwide [15,16,17]. In China, epidemiologic and clinical studies have reported that the overall malignant transformation rate of OSF is 1.2 to 2.2% [9]. In India, around 7.6% of OSF patients develop oral cancer [8,18]. Based on our survey of articles available in PubMed, Google Scholar, and Medline, we found no information on the malignant transformation rate of OSF in Vietnam. The malignant transformation rate of OSF in Taiwan is about 3.27–23% [3,17,19,20]. The varying malignant transformation rate of OSF may be due to the different ages, sex, tracking period, risk factors, and pathological diagnosis of the studies. However, these studies show that OSF patients are at risk of developing oral cancers. Previous studies have proven that the duration of OSF and the degree of worsening of symptoms directly correlate with the progression to oral cancer. According to statistics, OSF generally progresses to oral cancer 3–16 years after the OSF diagnosis [15,21].

Risk Factors of OSF

Immunologic causes (inflammation and autoimmunity) contribute to OSF, along with nutritional factors (vitamin B, C, and iron deficiency), carcinogenic causes (chewing tobacco and betel nut), alcohol, and consumption of spicy food, epigenetic regulation, and genetic predisposition. Overconsumption of chili-containing food irritates the oral mucosa that may cause an inflammatory response to induce OSF. However, in Mexico and America where chili is widely used, OSF is not found. Regarding nutritional deficiency, OSF patients show significantly lower levels of serum β-carotene, iron, vitamin C and, zinc in a grade dependent manner; all these factors are known to negatively affect the wound healing process. Conversely, the patients also have higher serum levels of copper that enhance the lysyl oxidase (LOX) activity of cross-linking collagen fibers and elastin. The increase in salivary copper concentration is reported to be associated with increasing clinical grade. Epigenetic alteration had been observed in Wnt inhibitory factor-1 (WIF1) and p16 genes of the buccal cells in OSF patients. Hypermethylation of these two genes also contributes to the potential malignancy of OSF.

Differential Diagnosis of OSF: Understanding the progression of the OSF can help to determine the appropriate treatment. Because of advancements in biotechnology, the research on OSF biomarkers has become more and more vigorous, which is helpful for the diagnosis of OSF and malignant transformation.

OSF Classification by Function

Various staging/grading classification systems of OSF have been documented in the past, such as

clinical, functional, and histological staging/classification of OSF. Most systems include three staging/grading classifications according to the mucosa status, fibrous bands, and mouth opening. Some of the staging systems are used by doctors in the clinic to diagnose or treat OSF. According to clinical staging/classification, patients with early OSF show stomatitis and vesiculation; those with moderate OSF show a marble-like appearance and palpable fibrous bands; and those with severe OSF show leukoplakia and erythroplakia in the lesion.

SF Classification by Histology

It is worth noting that the OSF can transform to oral squamous cell carcinoma (OSCC), and that solid biopsy is needed for clinical diagnosis and treatment. In histological staging/classification, the amount and distribution of fibroblasts, collagen fibers, inflammatory cells, and blood vessels is used to determine the various stages of OSF. Generally, OSF is classified into four histopathological stages. The pathological characteristics are chronic inflammation and excessive collagen deposition in the connective tissues below the oral mucosal epithelium, accompanying local inflammation in the lamina propria or deep connective tissues, and degenerative changes in muscles. Generally, epithelial atrophy, and loss of rete pegs are also reported

The Mechanism of OSF Pathogenesis and Malignant Transformation

OSF is prevalent in Asia, and the main risk factor is betel nut chewing. The clinical biomarkers indicated the inflammation reaction and collagen deposition disorder contribute to OSF. Clinical data showed identical biomarkers in late-stage OSF and malignant transformation tissues. It may interpret some parts of the mechanisms of how OSF transform into malignancy. In this section, we integrated the clinical findings and animal studies to have a profound understanding of the etiology.

Pathogenesis of OSF

OSF is mainly induced by areca nut chewing in Asia. The main components of areca nut contain 31.1% phenols, 18.7% polysaccharides, 14% fat, 10.8% fiber, and 0.5% alkaloids. Arecoline is the main alkaloid that causes the pathogenesis of the OSF. Arecoline stimulates the fibroblast cells to express growth factors and cytokines that enhance the collagen deposition and repress the collagen degradation. Clinical studies reported transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), beta fibroblast growth factor (bFGF), alpha-smooth muscle actin (α-SMA), tumor necrosis factor-α (TNF-α), serum c-reactive protein, ROS level, matrix metalloproteinases (MMP), and the tissue inhibitors of metalloproteinases (TIMP) were expressed abnormally in OSF group. Arecoline activates the oral tissue express TNF-α that stimulates cell inflammation. Cell inflammation will activate the wound healing reaction, which decreases MMP and increases TIMP expression. This TIMP and MMP expression profile is also found in the oral tissue of OSF patients. The function of MMP is to degrade the extracellular matrix protein, and TIMP inhibits this process. This contributes to the abnormal collagen deposition on the lesion. Inflammation reaction also stimulates the cell express bFGF and TGFβ-1. Continuously overexpressing bFGF in oral cells contributes to the collagen deposition disorder in OSF. TGFβ-1 stimulates fibroblasts to transform to myofibroblasts, which are mainly responsible for collagen production and wound contraction. Normally, myofibroblasts undergo apoptosis after finishing the mission of wound healing. However, this mechanism is disrupted in OSF. Arecoline also increases the ROS level in OSF patients'

serum. Serum ROS attacks the structure of the blood vessels in endothelial cells, induced cell senescence, and DNA double-stranded breaks. The decrease in blood flow around the oral mucosa finally causes one of the pathological symptoms - epithelial atrophy. The cell inflammation reaction and ROS attack stimulate the cell to activate the TGF-β signaling pathways. The TGF-β signaling is responsible for ceasing the cell cycle and promoting apoptosis in the unrepaired damage cells while the cells are damaged by stimulants. TGF-β also activates the downstream gene, CTGF, expression to promote the fibroblast-mediated production of extracellular matrix deposition. In addition, copper participates in the cross-linking of collagen. It enhances the hardness of the oral submucosa tissue and exacerbates the limitation of mouth opening and trismus. The commercial areca nut was reported to contain a significantly higher level of copper than the raw areca nut. Higher serum copper was also found among OSF patients and was deemed as one of the factors that induce OSF.

Transformation of OSF to Malignancy

OSF is deemed as a pre-malignant phenotype of OSCC. However, a cross-sectional multi-central study in Pakistan, from 2004 to 2012, showed that among 1774 patients, 26.6% had malignant transformation of OSF to OSCC, and 30.27% had OSCC without clinically visible OSF. Another study reported the potential malignant rate of OSF to be 7–30%. This reveals that one-third of OSF cases have a chance to turn into malignancy. The mechanism underlying the transformation of OSF to OSCC is still unclear. Researchers conducted a clinical observational study to identify molecular biomarkers from patient specimens and detect a possible link between OSF and OSCC. Wound healing is a process that helps the human body repair tissue damage. However, persistent inflammation, collagen deposition, growth factors, and cytokine secretion induced by arecoline may lead to malignancy. TGF-β activation in late-stage cancer can promote tumorigenesis, including metastasis and chemoresistance. CTGF is involved in epithelial-mesenchymal transition and angiogenesis. TNF activates distinct signaling pathways to decide the cell fate; the nuclear factor-κB (NF-κB) pathway contributes to cell survival, and the c-Jun N-terminal kinase pathway contributes to cell death. TNF-α is reported to stimulate cancer cell growth, proliferation, invasion, and metastasis. MMPs have been reported as one of the main factors of cancer progression and metastasis formation. Carcinogenesis has four main phases, including initiation, promotion, progression, and metastasis. Normal cells are exposed to carcinogens that induced DNA damage, as well as dysregulate cellular proliferation, survival, differentiation, and the DNA repair function. Areca nut, tobacco, and alcohol are the three main carcinogens in oral cancer. In vitro and in vivo studies have revealed that arecoline and areca alkaloid induced mutagenicity in vitro and carcinogenicity in vivo. A clinical observational study showed the potential for malignant transformation of OSF cases in individuals consuming both areca nut and tobacco consumption. The promotion stage is a lengthy and irreversible process. This is a phase between a pre-malignant lesion and the development of malignant tumors. Once the patient suffers from OSF, limitation of mouth opening and burning sensation compel them to seek medical help. Medical intervention and eliminating the use of the carcinogens effectively interrupts the malignant promotion process. This may explain why the clinical malignant transformation rate of OSF is at most 30% rather than 100%. Clinical studies also proved that prolong areca nut and tobacco use induced malignant transformation.

From the other point of view, change of the microenvironment around the fibrosis tissue is also a malignant promotion factor. While the collagen deposition alters in oral mucosa, the compact tissue oppresses the capillaries and block the blood flow that produces a hypoxic environment suitable for the promotion of malignant cell growth. Virus infection may be one factor that induces OSF malignancy. Human papillomavirus types 16 and 18 are well-known viruses that cause oral cancer. OSF patients have a higher infection rate of human papillomavirus (HPV) than the normal group, which could explain the potential malignancy of OSF.

OSF and Malignancy Formation-The Evidence on Animal Models

Building an animal model is crucial for investigating the mechanism of OSF formation and malignant transformation. Early in 1997, Huan et al. established an animal model using Sprague-Dawley (SD) rats; they either injected or applied aqueous areca nut extracts (AANE) to buccal mucosa and successfully induced the collagen deposition in the buccal mucosa. The common animal species used in OSF animal models are SD rats and BALB/C mice. Usually, males are used to avoid the effects of hormone fluctuations. All the studies use chemicals in areca nut as a material, including areca nut water extract and arecoline. These studies are all conducted in Asia. Some studies inject the water extract into the subcutaneous region, while others topically applied the water extract onto the surface of buccal mucosa followed by fasting for 2 hrs. Other studies added the water extract into drinking bottles. The dosage depends on the purity of the compound and the method of administration. Topical arecoline applied at 8 mg/mL could effectively induce OSF. If the AANE is administered through a water bottle, the concentration is much higher.

Treatment Strategy

OSF contributes to the hardness of submucosa tissue. It jointly affects the muscles, bones, and joints movement below the submucosa tissue, which will eventually affect the degree of mouth opening and results in trismus. Limitation of the mouth opening makes it difficult in daily routine oral cleaning, speaking, and eating. Combining the annoying symptoms like burning sensation and xerostomia, patients' quality of life is low. The goals of clinical treatments are relieving the annoying symptoms and improving mouth opening to elevate the patients' quality of life. The current treatment methods for OSF are mainly divided into three categories: drug treatment, mouth opening exercising, and elective surgery. However, there is no standardized treatment protocol for clinicians. In this section, we summarize the commonly used drugs, types of exercise devices, and types of surgeries mentioned in the recent literature.

Physical Therapy

Hyperbaric oxygen therapy (HBOT) is used to treat decompression sickness, gas gangrene, and carbon monoxide poisoning. In HBOT, the patient is placed in a hyperbaric chamber in which the ambient oxygen pressure is higher than atmospheric pressure. HBOT was first applied in dentistry in 1988 to promote periodontal wound healing. Recently, the application of HBOT in OSF was reported. HBOT enhances fibroblast apoptosis and inhibits fibroblast activity by reducing IL-1β and TNF-α production. HBOT attenuates the production of proinflammatory cytokines such as IL-1, IL-6, and IL-10. HBOT enriches oxygenation of all tissues and hinders the production of reactive oxygen species such as E-SOD, GPx, catalase, paraoxonase, and heme-oxygenase-1. HBOT suppress fibroblast activity,

has anti-inflammatory and antioxidant properties, thus resulting in the therapeutic effect of OSF.

Drug Therapy

The main objectives of drug therapy for OSF are anti-inflammation and degradation of the extracellular matrix. Corticosteroids comprise a class of steroid hormones produced in the vertebrate adrenal cortex. Many of them have been synthesized. The glucocorticoids and mineralocorticoid participate in numerous physiological and biochemical processes. Glucocorticoids block inflammation mediators and impede the inflammatory reaction. They also block fibroblast proliferation and collagen deposition. Dexamethasone, methylprednisolone, and betamethasone are synthetic drugs with glucocorticoid-like effects. Intralesional injection of synthetic corticosteroids significantly improves mouth opening and alleviates the burning sensation in OSF. Hyaluronidase and chymotrypsin are proteolytic enzymes that degrade extracellular matrices such as hyaluronan and collagen. They are usually co-administered with corticosteroids in OSF treatment. Pentoxifylline is a xanthine derivative primarily used to mitigate muscle pain. It competitively and nonselectively inhibits phosphodiesterase, suppresses TNF-α production in lipopolysaccharide (LPS)-stimulated human monocytes, blocks leukotriene synthesis, and diminishes the inflammatory reaction. Pentoxifylline improved mouth opening and reduced the burning sensation in OSF. It also facilitated swallowing and speech. Colchicine has been used as early as 1500 BC to treat joint swelling. It was approved for medical use in 1961. It is extracted from the autumn crocus and decreases inflammation by inhibiting neutrophil activation and migration to the inflammation site and by suppressing IL-1 β activation. The efficacy of colchicine in OSF treatment was first reported in 2013. Patients with OSF took 0.5 mg oral colchicine twice daily and received injections of 1500 IU hyaluronidase into each buccal mucosal lesion once weekly. By the second week, the burning sensation was alleviated, mouth opening increased, and histological parameters were reduced. The aforementioned dosages combined with 0.5 mL lignocaine hydrochloride once weekly improved mouth opening and reduced the burning sensation in patients with grade II OSF after 12 weeks.

Screening models for submucosal fibrosis:

1. **Clinical Symptoms and History**

- **Symptoms**: Patients may experience symptoms such as difficulty swallowing (in esophageal fibrosis), chronic pain, digestive problems, or breathing difficulties (in cases involving the lungs).
- **Risk Factors**: A history of chronic inflammation, autoimmune disorders, infections, or diseases like eosinophilic esophagitis, Crohn's disease, or systemic sclerosis may increase the likelihood of submucosal fibrosis.

2. Screening Tools and Imaging Techniques

Several screening models and diagnostic techniques are employed to detect submucosal fibrosis. These include:

- **Endoscopy and Biopsy**: Endoscopic evaluation allows physicians to visually assess the tissue for signs of fibrosis. A biopsy may be taken to examine the histological features of the submucosal layer and confirm the presence of fibrosis.
- **Endoscopic Ultrasound (EUS)**: EUS is a non-invasive imaging technique that provides detailed images of the layers of the

gastrointestinal wall, including the submucosa. It can assess the thickness of the submucosal layer and help in identifying fibrosis.

- **Magnetic Resonance Imaging (MRI)**: In some cases, MRI may be used to assess fibrosis in organs like the lungs or esophagus, particularly when looking for structural changes.
- **High-Resolution Computed Tomography (HRCT)**: This imaging technique is particularly useful in diagnosing pulmonary fibrosis. It provides detailed views of lung architecture and can identify submucosal changes.
- **Elastography**: A relatively newer method, elastography measures the stiffness of tissues. Since fibrosis increases tissue stiffness, this technique can help identify submucosal fibrosis, especially in liver, lung, or gastrointestinal diseases.

3. **Biomarkers**

- **Blood Tests**: Some biomarkers in the blood may indicate the presence of fibrosis. For example, elevated levels of specific proteins or cytokines may reflect inflammatory processes or fibrosis. However, these markers are generally more useful for monitoring disease progression rather than providing a definitive diagnosis.
- **Gene Expression Profiling**: In some research settings, gene expression patterns associated with fibrosis are being studied. These tests may help in early diagnosis or in determining the severity of the condition.

4. Fibrosis Scoring Systems

In clinical practice, scoring systems are used to quantify the degree of fibrosis based on imaging, histology, or clinical presentation:

- **Ishak Scoring System**: Often used in liver diseases, this system grades fibrosis based on histological features.
- **METAVIR Score**: A widely used system for assessing liver fibrosis, using liver biopsy or imaging tests to rate fibrosis severity from F0 (no fibrosis) to F4 (cirrhosis).
- **Eosinophilic Esophagitis Scoring**: For esophageal fibrosis, a system that evaluates the degree of submucosal fibrosis can be employed, combining endoscopic and histological findings.

5. **Histopathology**

- **Collagen Deposition**: One of the key features of submucosal fibrosis is the excessive deposition of collagen fibers. Histological examination of tissue samples can confirm fibrosis by showing thickened submucosal layers and increased extracellular matrix components.
- **Inflammatory Markers**: Chronic inflammation, as seen in conditions like eosinophilic esophagitis or inflammatory bowel disease, is often present alongside fibrosis. Biopsy specimens can reveal the presence of inflammatory cells in the submucosa.

6. **Management of Submucosal Fibrosis**

- **Early Diagnosis**: Early detection of submucosal fibrosis allows for the management of underlying causes, such as treating chronic inflammation or autoimmune conditions.

- **Therapeutic Options**: In some cases, fibrosis can be partially reversed by treating the underlying disease or using antifibrotic medications. In other cases, surgical interventions like dilation (for esophageal fibrosis) may be necessary.
- **Monitoring Disease Progression**: Regular monitoring using imaging or biopsies is important to track the progression of fibrosis and assess treatment effectiveness.

7. Emerging Technologies

- **Artificial Intelligence (AI) in Imaging**: AI is being integrated into imaging techniques to help identify submucosal fibrosis with greater accuracy, even in cases where fibrosis is not easily detectable by the human eye.
- **Non-invasive Biomarkers**: New research is focused on identifying non-invasive biomarkers (e.g., blood tests) for fibrosis detection, which could potentially replace more invasive procedures like biopsies.

CONCLUSIONS

The prevalence of OSF and the rate of malignant transformation are different among countries. Quitting betel nut chewing is the best strategy to prevent OSF and potential malignancy. Regardless of the strategy, clinical diagnosis and treatment are still based on conservative methods. The treatment must improve the elasticity of the oral mucosa and mouth opening distance. This ensures that patients have normal oral functions like speaking and eating to improve the patient's quality of life and provides an adequate nutritional intake. High-quality clinical studies are needed to help clinicians to develop and apply molecular biomarkers and to formulate standard treatment guidelines for OSF. Nutritional deficiencies may not play a primary role but it could synergies the symptomotology by contributing to epithelial atrophy. Although the involvement of HLA and genetic predisposition has been reported, specific haplotypes have not been determined. The individual mechanisms operating at various stages of the disease–initial, intermediate and advanced–need further study in order to propose appropriate therapeutic interventions.

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