Review Article

Current state of research, diagnosis, staging and outcome of oral submucosal fibrosis

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ABSTRACT

Oral submucosal fibrosis (OSMF) is an Areca nut induced, proliferating oral disease found in Southeast Asian regions including India, affecting millions. The limited collective wisdom prevailing in the understanding of OSMF is ineffective in the management of the disease. A tentative disease grading strategy, the iterations of which are periodically published, is used by dentists, oral surgeons, and clinicians, in general, to determine the severity of OSMF. The lack of recognition of a single authoritative staging system compounded by the unavailability of an unbiased measurement tool presents a diagnostic problem. The review presents a case for implementing higher standards of clinical research and the need to correlate various disease parameters with the appropriate disease stage for effective therapeutic approach. Given the irreversible nature of the fibrotic process in advanced stages, the complications of OSMF are discussed in addition to patient compliance issues. A perspective on the potential of future OSMF initiatives is also presented.

Key words: OSMF, collagen metabolic disorder, fibrous bands, areca, gutka, pan-masala, arecoline, tobacco

INTRODUCTION

Oral submucosal fibrosis (OSMF) is a slow developing, yet proliferating oral disease found throughout Southeast Asian regions, affecting over 5 million individuals in India alone in the previous decade.[1-4] OSMF is largely attributed to abuse of Areca nut products.[2,3,5-7] Among the clinical findings of this disease are moderate-to-severe restriction of the mouth opening, palpable fibrous bands spanning the cheeks, inflammation of the oral tissues, blanching of cheek inner walls, soft palate and buccal labia, shrinking and rigidity of tongue, uvula, etc. The clinical features routinely occur along with leukoplakia, lichenoid reaction, lichen planus, and verrucous lesions.[2,3,5,7-9] OSMF case reports also indicate hearing loss in some individuals.[10,11] The symptoms result in poor oral health, sensitivity to spicy foods, and lowering of the quality of life due to poor mouth opening. Without intervention and continued abuse, Areca product exposure dramatically increases the probability of the OSMF patient to develop oral malignancy. Early surveys conducted to evaluate the threat of Areca chewing habit-related malignancy, placed the risk at 7.6% of OSMF cases.[2,5,12-16] Subsequent small-scale surveys yielded similar low-risk figures;[16] however, more recent work reports that 22–30% of OSMF patients tend to transition to oral malignancy.[3] Such higher risk figures are further supported by long-running studies carried out in Vadodara, Gujarat, endemic for OSMF cases, due to widespread abuse of customized *Areca* nut preparations (Personal communication - Dr. C. M.).

Higher grades of OSMF Stages III and IV are virtually unretractable and currently require surgical excision[2,3,8,13,16] which has limited prospects of recovery.

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The current clinical judgment and treatment for OSMF have not been scientifically established despite numerous publications elucidating a variety of therapeutic and surgical approaches.[3,17-20] Reliable OSMF diagnostics are an unmet need in India and may help prevent a sizable population from being impoverished by burgeoning medical costs. At present, varied disease staging criteria[8,19-24] are used by clinicians with only simplistic consensus, relying majorly on macroscopic traits such as mouth opening and presence of tissue blanching. These techniques are highly subjective and depend on the skill of the clinician/researcher. The problem is compounded due to the nature of the disease reporting and the consequent inability for early warning/detection for at-risk individuals/communities. The approach to OSMF therapy is largely explorative with poor documentation of post-therapeutic or post-operative recovery, which may be attributed to the poor follow-up by Indian patients. Higher grades of OSMF do not respond to therapeutic solutions and at times even surgical intervention, due to the aggressiveness of the fibrosis and its precancerous, hyperplastic tendency. Consequently, it is the opinion of OSMF-experienced clinicians that Stage IV OSMF is practically untreatable in the current state of disease management avenues. Being an endemic disease relegated to Southeast Asia which affects largely the poor segments of the Asian population, it has not received the active attention of researchers beyond the region. In our assessment, the typical patients of OSMF are the underprivileged individuals who will not or cannot address oral health issues which they encounter. The lack of awareness of OSMF which is endemic in the community compounds the health risk. The poor patient compliance, lack of disease awareness among the masses, poor documentation of OSMF cases, their amelioration, and subsequent follow-up complicate the systematic assimilation of knowledge or collective wisdom which we may gain from individual cases. Poor scientific methodology obfuscates the etiological findings. An overabundance of repetitive case reports and mere compilation type reviews do not further our understanding of OSMF. The present review attempts to address these issues, revisit disease grading of OSMF, and its status in India.

PRESENTATION OF OSMF CASES

Presentation of OSMF patients is perhaps the most discussed area in published clinical research on OSMF. Despite an authoritative grading system published by Pindborg and Sirasat[13] and Khanna and Andrade,[8] numerous iterations of the same, focusing on readily measured indices have been published.[17-26] A large number of OSMF-related publications are case studies of individuals delving into the possible grading and subsequent surgical treatment of the cases with or without the administration of therapeutic alternatives. While some researchers tend to narrow down clinical parameters to suit rapid identification,[23] the virtual lack in distinction of grading indices may be more confounding then helpful. Constructed from a consensus of rational OSMF grading schemes,[5,8,13] Figure 1 depicts the evolution of OSMF in the absence of medical intervention.

Figure 2 shows a representative distribution of mouth aperture parameters across a population of individuals with both healthy and OSMF/ osteomyeltis (OM) patients. Normal or non-OSMF patients demonstrate a significantly greater mouth opening as compared to the OSMF cases with the average mouth opening peaking around 50 mm. The representative data pooled

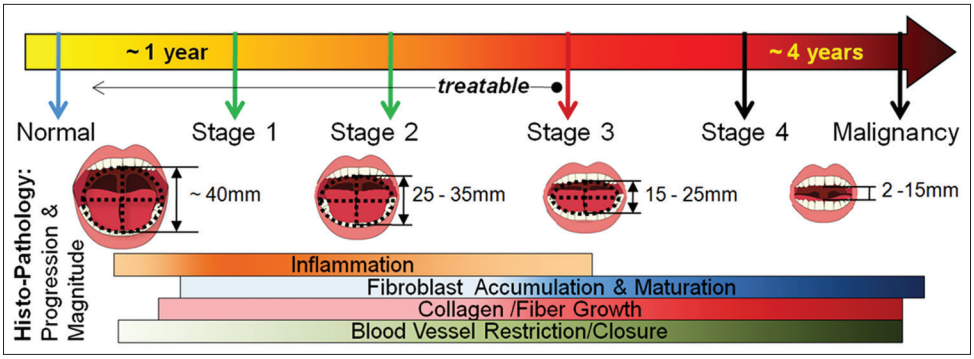

Figure 1: Consensus grading of oral submucosal fibrosis (OSMF) and codeveloping disease traits. From the beginning of substance abuse, OSMF evolves over roughly 4 years to fully emerge in Stage IV, assuming consistent use. Subsequent complications involve malignancy

information from multiple sources[2,5,16,27-29] across age and gender groups to create a general model of OSMF disease grade distribution in the Indian population. Interestingly, this model is biased in the sense that the data are generally dependent on the willingness of the patient to consult a clinician. Based on Figure 2, it appears that a majority of the patients presented with Stages II and III OSMF.[5,28,29] The pathological developments in Stage I may perhaps appear insufficiently alarming to a majority of the patients to avail clinical intervention. As demonstrated in Figure 2, between the Stages I and II, inflammatory changes peak and secondary events are initiated; collagen disorders and fibroblast accumulation are noted. Slow obliteration of blood vessels begins, aggravating the condition and possibly causing pain and discomfort to the patient. A hallmark of the disease, namely steady constriction on the mouth opening, begins to develop in this phase. The reduction in mouth opening and/or a combination of the symptoms above may, thus, be likely to motivate the OSMF patient to seek clinical help.

Based on an observation by Angadi and Rao[2] and Angadi and Rekha,[16] Areca abuse tapers off to some extent for the larger population, and the reluctance in consumption of the OSMF inducing agents leads to reduction in the risk development of OSMF. It is conceivable that the discontinued use of Areca leads to a significant reduction in the number of cases presenting with Stages III and IV, with or without superimposed OM.

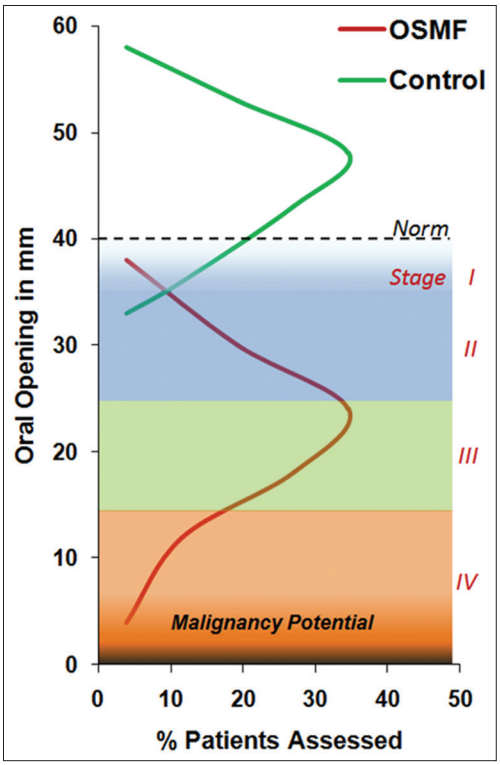

Figure 2: Distribution of maximum oral aperture in oral submucosal fibrosis (OSMF) and non-diseased sample population and frequency analysis of OSMF grades

NATIONAL STATUS OF OSMF

Tilakratne *et al*. reported a roughly 10-fold rise in the number of OSMF cases reported in the period between 1980 (~0.25 million cases) and 1993 (~2 million cases) within India.[9] A subsequent survey from 1996 as given by Aziz[4] stated a global prevalence number in the same range; however, with over 2 million OSMF cases in India alone, the claim may be severely underestimated. According to Chiu *et al*., over 5 million cases were documented in India by 2002; subsequent years did not yield updates on the global incidence of OSMF.[1]

Based on previously estimated figures, a conservative trajectory is drawn up to predict the number of OSMF cases in India by 2020 [Figure 3].[1,4,9] Restricting the exponential growth bias for the abuse of Areca nut products and subsequent OSMF cases, the projected incidence of the disease in India may well be around 16 million cases. Government intervention may play a role to curb the exponential rise, such as the gutka ban enacted in 2002 (Notification No. PFA/574-2002/7, by the Commissioner for the Food and Drug Administration and Food (Health) Authority and then again in 2012 under the aegis of the federal Food Safety and Regulation (Prohibition) Act 2011 and subsequent enforcement.[30,31]

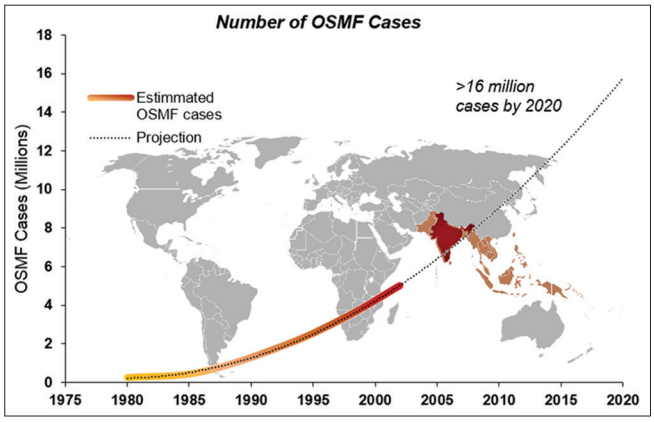

Figure 3: Incidence of oral submucosal fibrosis (OSMF) in India - gross estimates and projected cases. The solid line depicts the published estimated cases of OSMF. The dotted line is a conservative projection of OSMF cases. The true value of OSMF incidence may be significantly higher

Given its South/Southeast Asian bias, Areca is likely consumed currently, by close to a fifth of the population of the world in at least one of many preparatory forms; Gupta and Warnakulasuriya[7,32] suggest that the particular chewing habit is maintained by about 600 million individuals globally at a time when the global population was about 6300 million individuals.[33] It may be argued that the estimates reported in literature are thus conservative in nature and that the true incidence of OSMF is significantly greater. The underreporting of OSMF cases is an obstacle in documenting the national status of OSMF and indeed the global status, given the developing nature of most Southeast Asian countries. OSMF survey updates reporting national figures have not been conveyed over nearly two decades. Severe limitations like these create barriers not only in gauging the current disease status but also indeed in enabling clinicians to better treat OSMF and in promoting disease awareness among the masses. Several studies attempt to correlate the chewing habits of Areca products and their numerous combinations to the incidence of OSMF and oral cancer.[5,7,12,14-16,22,26,28,29,34] The complex nature of the etiological factor such as the total duration of chewing habit, frequency of chewing (per day), and the exposure period during individual consumption sessions comprises a singularly complex variable; the brand and amount of each type of product consumed add to the difficulty of the investigation. Angadi and Rekha demonstrate a self-limiting behavioral aspect of the Areca chewing habit.[16] While the largest number of cases is observed in the early productive age group, the abuse tapers off in later years and decades. The productive age group Areca abuse behavior is also documented by other researchers and may suggest peer pressure in environments for the new working-class individual.[5,13,14,16,21,27,28] A habit-forming aspect of Areca chewing is described in many articles on the subject of Areca abuse. Areca alkaloids, namely Arecoline and to a smaller extent Arecaidine, are reported to be weak muscarinic (M1 and M3) and nicotinic agonists.[4,35-38] It is interesting in this perspective that Areca abuse, as a habit, tapers off as described by Angadi and others.[16] A study by Khan *et al*. attributes the popularity of commercial Areca preparations to the flavoring and sweetening agents rather than the alleged stimulant or habit-forming aspects.[39] However, the cases investigated were minors and the data may have to be evaluated carefully for age bias.

Perhaps, the most worrisome aspect of the OSMF epidemic is the exposure to children. Multiple studies have testified to the prevalence of OSMF, often in high grades, in children between 6 and 11 years old.[39-43] These cases are particularly associated with Areca nut preparations such as gutka (banned, but still available),[30,44] pan masala, pan parag, and mawa. Few studies have attempted to document the plight of children exposed to Areca and OSMF *en masse*.[39,40] Khan *et al*.[39] cited the flavoring and sweetening agents as the primary motivation for rural children in Pakistan to consume the Areca products, followed by peer pressure, etc. A similar investigative study within India would reveal the undercurrent of substance abuse in our most vulnerable population segment. It should be noted that harboring high-grade OSMF at a young age does not bode well in terms of recovery and recuperation post-OSMF surgery. The aggressive nature of the collagen disorder is debilitating; moreover, since the at-risk children belong predominantly to the poor sections of society, affordability of medical care is an issue, possibly aggravating the disease over time.

RISK DEVELOPMENT IN OSMF

As covered elsewhere in this discussion, the precise etiology of Areca nut in the development of OSMF is rather complex; it factors in the total duration of chewing habit, frequency of chewing (per day), and the exposure period during individual consumption sessions. The amount and brand of the Areca product also matter in the overall phenomenon. The high variability in these parameters based on the preferences of the individual user, in turn, yield variable results. The inconsistency of Areca exposure is likely to result in the contradictory results reported in literature.[18,45,46] The phenomenon is reflected in the profile of OSMF case presentation such as that seen in Figure 2. Based on the data discussed in multiple reports in literature, a pattern develops showing protracted Areca exposure resulting in radically changing the OSMF presentation profile.[8,16,19,27-29,47] Figure 4 depicts the above profile shift; early users of Areca (short exposure) demonstrate a peaked response as seen in Figure 2. As the exposure period increases, the response shifts right with an observable decrease in number of cases of Stages I and II OSMF. On analysis of the longest documented Areca exposure (10 years), the profile shows the farthest right shift with majority of the cases presented being in Stage IV.

The implication of the information revealed by Figure 4 is that poor public/patient awareness of the health risks of Areca coupled with reluctance of patients to consult timely clinical help result in steady worsening of OSMF. Without intervention or habit cessation, OSMF keeps aggravating till it achieves Stage IV and possible cancerous status. Later stages of OSMF are particularly aggressive and difficult to

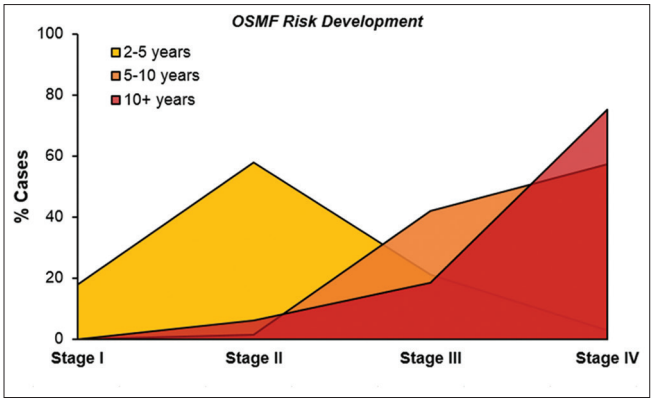

Figure 4: Exposure period-dependent risk development in oral submucosal fibrosis. Early Areca habit demonstrates the yellow profile with majority of cases reported in Stage II. Longer exposure causes the profile to shift right (orange and red) with a majority of cases in Stage IV

normalize, complication treatment.

Several additional components have been discussed in literature as having roles in OSMF development, such as chilies, slaked lime (calcium hydroxide), catechins, and tannins.[2,3,9,12,17,48,49] However, these need to carefully analyze to exclude misidentification. A systematic study to eliminate complicating variables will conclusively identify the primary etiological agent. Collusion of Areca products with tobacco is unavoidable, however, the association of Areca products with the results of tobacco abuse may generate confounding inferences. A distinction has to be made between the effects of the two and their habit-forming tendencies. As discussed elsewhere in this review, Areca products have mild muscarinic and nicotinic agonist aspects and are not known to be particularly habit forming by themselves. Similarly, the implication of chilies or capsaicin in OSMF appears fallacious; in that, the Indian population routinely consumes large amounts of chilies on a daily basis. It may seem more likely that chilies exacerbate the inflammatory reaction which peaks between Stages I and II OSMF, rather than precipitate an independent disease mechanism by themselves. Similarly, nicotine from tobacco and the caustic nature of calcium hydroxide are also counter indicated in the development of OSMF, based on early results by Patil *et al*. (unpublished work).[50]

STATUS OF RESEARCH ON OSMF AND ARECA HABIT-INDUCED ORAL CANCER

A significant body of work on the probable mechanisms and pathways of disease development have been published over the past few years. Several high-profile research papers and reviews on the subject implicate inflammation, altered collagen metabolism involving over-expression of collagen fibers, their systematic enlargement, down-regulated catabolism, fiber cross-linking, etc.[2,3,6,36,51-56] More simplistic research on the nature of collagen fibers has shown positive correlation of fiber thickening to disease grade; the orientation of fibers has also been shown to be influenced by a combination of Areca habit and vertical mastication motion of the mandible.[57,58] This may well be the primary reason behind the formation of the characteristic vertical fibrous bands which are seen in higher grades of OSMF.

Analysis of Areca nut products and attempts to correlate the chemical constituents with OSMF led to the development of the hypothesis implicating copper a potential etiological agent.[2,3,48,49,59-62] It should be noted that tamarind seeds consumed in parts of Maharashtra and Karnataka have also been implicated in literature for causing OSMF; while it has no known Arecoline-type alkaloids, it does contain copper. Reports of copper ions found in saliva samples also raised the possibility of being identified as an etiological agent. Trivedy *et al*., for instance, cited a relatively minor increase in tissue copper as their case.[62] Mohammed *et al*. working on this premise tested the correlation of salivary copper content and disease grade[45] but found no association between the two. Implication of copper as an etiological agent is particularly interesting when considering the fact that copper is used as the primary contraceptive agent in intrauterine devices such as the copper-T. Copper release kinetics show an average of 40 µg/day exposure to mucosal epithelia in the uterus for up to 3 years or more.[63] It is interesting in this perspective that copper-based intrauterine devices are not associated with incidences of fibrosis or any report of collagen/extracellular matrix disorder. These contradictory factoids raise doubt about the involvement of copper in the OSMF disease process. While research is still ongoing in this area, all the information on involvement on copper ions taken together may be considered as a cautionary tale and future work may require a systematic study design to avoid unsubstantial claims.

In a similar vein as above lies the central phenomenon of malignant transformation of OSMF to oral cancer. While the phenomenon presents in the context of OSMF frequently, laboratory research has contradicted the association in a few instances.[18,46] A 17-year association study[12,14] determined the malignancy rate at

7.6%, a majority of subsequent papers emulated these values.[16,28,64] The malignant transformation is virtually undisputed in clinical circles; however, the issue of poor diagnosis/classification, poor patient compliance factored with poor documentation protocols results in egregious underreporting. As Arakeri and Brennan[3] observed, the updated malignancy potential is much higher (22–30%), supported by other ongoing studies. This may be explained by the exponential growth in the commercial Areca product industry, improved logistics, blatant advertising, and esthetic and flavorful upgrading of Areca nut products. The industry is lucrative despite two government legislative acts and routinely risks legal/criminal punishment.[30,44,65] Researchers have to be wary of confounding factors in their study and map data after due diligence in diagnosis, staging, and documentation.

FUTURE PERSPECTIVES

As pinpointed earlier in this discussion, a status update for OSMF has been missing for the past 16 years. A clinical survey of OSMF cases, in depth and with proper follow-up, is the need of the hour. A special section is required to evaluate the children at risk with the rampant Areca abuse epidemic. With special reference to the risk shift on delay in disease intervention as shown in Figure 4, a public awareness drive is immediately required to educate the masses of the health risks of OSMF and oral cancer. This opportunity must be taken to reinforce the practical handling of OSMF diagnosis and therapy by clinicians. This must include a special note to document all OSMF and Areca-induced oral cancer cases. Little progress has been made in this area over the past few decades, consequently, misleading notions such as involvement of tobacco, chilies, and calcium hydroxide in OSMF. Oral submucous fibrosis is an insidious disease, as described by numerous OSMF reviews; however, the true threat of the Areca nut abuse is not communicated by words alone. Indeed, the disease creeps on the patients and debilitates the individual physically, socially, and emotionally.[7,65,66] The medical expenses accrued in the course of treatment, if sought at all, can be formidable for some. Conservative estimates put medical expenses at a few thousand rupees for a 6-month course at Stage I to several lakhs of rupees in surgeries, hospital stay, and medical bills for a repeat surgery Stage IV patient. Keeping in mind that OSMF is a poor man's disease for the most part, who seek late clinical help if at all, the therapy for OSMF is as debilitating for the individual as the disease itself. The costs reflected here do not factor in the loss of income. Areca abuse can, thus, be expressed truly as a social evil which feeds on the lowest segment of the population. It is sustained by the ignorance of the masses to its health hazards and a collective ignorance of the true agent of misery, Areca which is blatantly advertised, sold at a premium, and made widely available to the people, including children.

To address the OSMF epidemic, a national reporting scheme needs to be designed which can present initiatives to address ineffectual OSMF management. An OSMF board/panel could drive research and clinical community discussion to help stay abreast of meaningful developments, to dispel misleading notions such as involvement of chilies, slaked lime, or tobacco in OSMF. It may help promote a more scientific approach to understanding OSMF such as requiring a stronger rationale for biochemical analysis, improved analytical tools, and methods. In the face of lacking information, a national initiative (with or without government support) to aggregate OSMF/OM research, case documentation (with ethnicity, gender, and age bias reported in along with geographical association) is critical. Such an aggregator could be a national level OSMF board/panel of experts that could advise the state or central government regarding the amelioration of OSMF/OM. The clinical community involved with OSMF needs to move beyond historical perspective when publishing to adhere to highest standards of professionalism. A common addition found in most articles on OSMF is the repetitive allusion to ancient texts, early reports from 1952 by Schwartz *et al*. and quoting survey data from 1984 (the 7.6% malignancy rate by Pindborg *et al*.). These do not add to the modern discussion on OSMF and in fact stem from a collective attitude to relegate the discussion on OSMF to academic utility alone. Efforts must be taken to inculcate superior investigative attitudes, skills, and protocols and to avoid repetitive publication of known information, for instance, case reports of a well-characterized disease such as OSMF itself.

SUMMARY

Limited basic research in OSMF offers precious little insight into the disease mechanism, and consequently, very limited scientific lead is available to craft a viable therapeutic solution to the insidious clinical condition. While the disease itself is clinically explored periodically, little more than solitary case reports

are published. OSMF therapy, consequently, is experimental at best and in combination with surgery creates a financial burden for OSMF patients without true amelioration of the disease. The aggressive nature of the collagen disorder presents a formidable challenge for cure. However, systematic research will help elucidate the disease mechanism which, in turn, can be targeted to successfully treat a disease which is estimated to have at least 16 million victims in the immediate future. The problem of OSMF is a self-inflicted one and of an addictive substance abuse origin. Confounding factors abound, some born more from misconceptions than coincidence; care should be taken for systematic investigative study. OSMF would be best addressed by raising its awareness, removing the social stigma, and promoting oral health-care camps that guide victims toward better treatment and possible cure of the disease. Early detection and aversion from OSMF inducing products are currently the only viable remedy; however, ongoing research in some laboratories is poised to change the scenario in the near future. To this effect, greater emphasis on OSMF biological/biomedical research is the need of the hour.

REFERENCES

1. Chiu CJ, Chang ML, Chiang CP, Hahn LJ, Hsieh LL, Chen CJ, *et al*. Interaction of collagen-related genes and susceptibility to betel quid-induced oral submucous fibrosis. Cancer Epidemiol Biomarkers Prev 2002;11:646-53.
2. Angadi PV, Rao SS. Areca nut in pathogenesis of oral submucous fibrosis: Revisited. Oral Maxillofac Surg 2011;15:1-9.
3. Arakeri G, Brennan PA. Oral submucous fibrosis: An overview of the aetiology, pathogenesis, classification, and principles of management. Br J Oral Maxillofac Surg 2013;51:587-93.
4. Aziz SR. Oral submucous fibrosis: Case report and review of diagnosis and treatment. J Oral Maxillofac Surg 2008;66:2386-9.
5. Sinor PN, Gupta PC, Murti PR, Bhonsle RB, Daftary DK, Mehta FS, *et al*. A case-control study of oral submucous fibrosis with special reference to the etiologic role of Areca nut. J Oral Pathol Med 1990;19:94-8.
6. Scutt A, Meghji S, Canniff JP, Harvey W. Stabilisation of collagen by betel nut polyphenols as a mechanism in oral submucous fibrosis. Experientia 1987;43:391-3.
7. Bhisey R, Boucher B, Chen T, Gajalakshmi V, Gupta P, Hecht S, *et al*. WHO: International Agency for Research onCancer. Monographs on the Evaluation of Carcinogenic Risks Tohumans: Betel-quid and Areca-nut Chewing and Some Areca-nutDerivednitrosamines. Lyon, France: World Health Organization; 2004. p. 113-32.
8. 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.
9. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: Review on aetiology and pathogenesis. Oral Oncol 2006;42:561-8.
10. Devi P, Singh I, Setru R, Tyagi K, Singh D, Thiyam B, *et al*. Evaluation of hearing deficit in patients with oral submucous fibrosis. J Oral Sci 2015;57:109-13.
11. Shah M, Katarkar A, Shah P, Alam N, Modh D. Tympanometric study of eustachian tube function in oral submucous fibrosis. Indian J Otol 2011;17:80-2.
12. Pindborg J, Murti P, Bhonsle R, Gupta PC, Mehta FS, Daftary DK, *et al*. Oral submucous fibrosis as a precancerous condition. Eur J Oral Sci 1984;92:224-9.
13. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol 1966;22:764-79.
14. Pindborg JJ, Mehta FS, Gupta PC, Daftary DK. Prevalence of oral submucous fibrosis among 50,915 Indian villagers. Br J Cancer 1968;22:646-54.
15. Pindborg J. Oral submucous fibrosis as a precancerous condition. J Dent Res 1966;45:546-53.
16. Angadi PV, Rekha KP. Oral submucous fibrosis: A clinicopathologic review of 205 cases in Indians. Oral Maxillofac Surg 2011;15:15-9.
17. Hebbar PB, Sheshaprasad R, Gurudath S, Pai A, Sujatha D. Oral submucous fibrosis in india: Are we progressing?? Indian J Cancer 2014;51:222-6.
18. Pandya S, Chaudhary AK, Singh M, Singh M, Mehrotra R. Correlation of histopathological diagnosis with habits and clinical findings in oral submucous fibrosis. Head Neck Oncol 2009;1:10.
19. Shivakumar G, Sahana S. Clinical staging of oral submucous fibrosis: A review. Int J Oral Med Sci 2011;10:216-9.
20. Priyadharshni B. Classification system for oral submucous grading-a review. Int J Sci Res 2014;3:740-4.
21. Patil S, Maheshwari S. Proposed new grading of oral submucous fibrosis based on cheek flexibility. J Clin Exp Dent 2014;6:e255-8.
22. More CB, Das S, Patel H, Adalja C, Kamatchi V, Venkatesh R, *et al*. Proposed clinical classification for oral submucous fibrosis. Oral Oncol 2012;48:200-2.
23. More C, Gupta S, Joshi J, Varma S. Classification system for oral submucous fibrosis. J Indian Acad Oral Med Radiol 2012;24:24-9.
24. Jani Y, Dudhia B. The clinicohistopathologic study of oral submucous fibrosis: A new staging system with treatment strategies. J Indian Acad Oral Med Radiol 2016;28:111-8.
25. Passi D, Bhanot P, Kacker D, Chahal D, Atri M, Panwar Y, *et al*. Oral submucous fibrosis: Newer proposed classification with critical updates in pathogenesis and management strategies. Natl J Maxillofac Surg 2017;8:89-94.
26. Agarwal RK, Hebbale M, Mhapuskar A, Tepan M.

Correlation of ultrasonographic measurements, histopathological grading, and clinical staging in oral submucous fibrosis. Indian J Dent Res 2017;28:476-81.
27. Kumar S, Singh R. Pterygium excision and conjunctival autograft: A comparative study of techniques. J Indian Acad Oral Med Radiol 2016;28:124-8.
28. Hazarey V, Erlewad D, Mundhe K, Ughade S. Oral submucous fibrosis: Study of 1000 cases from central India. J Oral Pathol Med 2007;36:12-7.
29. Kiran Kumar K, Saraswathi TR, Ranganathan K, Uma Devi M, Elizabeth J. Oral submucous fibrosis: A clinico-histopathological study in Chennai. Indian J Dent Res 2007;18:106-11.
30. Times News Network-Chandramouli R Gutka ban Loss could be Rs 1500-Rs 2000 Crores. Chennai: Times of India; 2014. Available from: https://www.timesofindia.indiatimes.com/city/chennai/Gutka-ban-loss-could-be-Rs-1500-Rs-2000-crores/articleshow/16398290.cms. [Last accessed on 2018 Jun 23].
31. Express News Service FSSAI Enforces Supreme Court's ban on Gutka, pan Masala. Pune: The Indian Express; 2017. Available from: https://www.indianexpress.com/article/india/fssai-enforces-supreme-courts-ban-on-gutka-pan-masala-4887916. [Last accessed on 2018 Jun 23].
32. Gupta PC, Warnakulasuriya S. Global epidemiology of Areca nut usage. Addict Biol 2002;7:77-83.
33. United Nations Dept of Economic Social Affairs World Population 2002; 2002. Available from: http://www.un.org/esa/population/publications/wpp2002/wpp2002wc.htm. [Last accessed on 2018 Jun 25].
34. Barceloux D. Betel Quid and Areca Nut. Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants. Hoboken, New Jersey: John Wiley and Sons; 2012. p. 781-7.
35. Broadley K, Kelly D. Muscarinic receptor agonists and antagonists. Molecules 2001;6:142.
36. Papke RL, Horenstein NA, Stokes C. Nicotinic activity of arecoline, the psychoactive element of "Betel nuts", suggests a basis for habitual use and anti-inflammatory activity. PLoS One 2015;10:e0140907.
37. Wishart D. Arecoline-Drugbank. Canada: Wishart Group; 2008.
38. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, *et al.* DrugBank: A knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res 2008;36:D901-6.
39. Khan A, Siddqui H, Hasan T, Bashir S. Prevalence of Areca nut eating habits and incidence of oral submucosal fibrosis in school children-a prospective cross-sectional survey. Pak Oral Dent J 2014;34:462-6.
40. Shah SM, Merchant AT, Luby SP, Chotani RA. Addicted schoolchildren: Prevalence and characteristics of Areca nut chewers among primary school children in Karachi, Pakistan. J Paediatr Child Health 2002;38:507-10.
41. Kumar S, Srivastava A, Mohan C, Pagrani M. A 11-year-old boy with oral submucous fibrosis: A rare case report. Int J Med Public Health 2014;4:511-3.
42. Duggirala T, Marthala M, Gannepalli A, Podduturi S. Oral submucous fibrosis in children: Report of three cases and review. J Indian Acad Oral Med Radiol 2015;27:105-11.
43. Gupta VK, Malhotra S, Patil R, Tripathi A. Oral submucous fibrosis at pediatric age, now time to think: Series of two cases. Indian J Med Paediatr Oncol 2013;34:107-10.
44. Times News Network Gutkha Material Worth Rs 1 Crore Seized. Vadodara: Times of India; 2017. Available from: https://www.timesofindia.indiatimes.com/city/vadodara/gutkha-material-worth-rs-1-crore-seized/articleshow/57300619.cms. [Last accessed on 2017 Feb 23].
45. Mohammed F, Manohar V, Jose M, Thapasum AF, Mohamed S, Shamaz BH, *et al.* Estimation of copper in saliva and Areca nut products and its correlation with histological grades of oral submucous fibrosis. J Oral Pathol Med 2015;44:208-13.
46. Stich HF, Rosin MP, Brunnemann KD. Oral lesions, genotoxicity and nitrosamines in betel quid chewers with no obvious increase in oral cancer risk. Cancer Lett 1986;31:15-25.
47. Hosein M, Mohiuddin S, Fatima N. Association between grading of oral submucous fibrosis with frequency and consumption of Areca nut and its derivatives in a wide age group: A multi-centric cross sectional study from Karachi, Pakistan. J Cancer Prev 2015;20:216-22.
48. Arakeri G, Brennan PA. Dietary copper: A novel predisposing factor for oral submucous fibrosis? Med Hypotheses 2013;80:241-3.
49. Ekanayaka RP, Tilakaratne WM. Oral submucous fibrosis: Review on mechanisms of pathogenesis and malignant transformation. J Carcinog Mutagen 2013;S5:2.
50. Patil Y, Patil P, Khandare J. Critical Role of Areca Alkaloids in OSMF and Oral Cancer; 2018. (Manuscript in preparation).
51. Arakeri G, Rai KK, Hunasgi S, Merkx MA, Gao S, Brennan PA, *et al.* Oral submucous fibrosis: An update on current theories of pathogenesis. J Oral Pathol Med 2017;46:406-12.
52. Illeperuma R, Ryu M, Kim K, Tilakaratne W, Kim J. Relationship of fibrosis and the expression of TGF-& beta; 1, MMP-1, and TIMP-1 with epithelial dysplasia in oral submucous fibrosis. Oral Med Pathol 2010;15:21-8.
53. Khan I, Kumar N, Pant I, Narra S, Kondaiah P. Activation of TGF-β pathway by Areca nut constituents: A possible cause of oral submucous fibrosis. PLoS One 2012;7:e51806.
54. Moutasim KA, Jenei V, Sapienza K, Marsh D, Weinreb PH, Violette SM, *et al.* Betel-derived alkaloid up-regulates keratinocyte alphavbeta6 integrin expression and promotes oral submucous fibrosis. J Pathol 2011;223:366-77.
55. Nishioka T, Eustace A, West C. Lysyl oxidase: From basic science to future cancer treatment. Cell Struct Funct 2012;37:75-80.
56. Rajalalitha P, Vali S. Molecular pathogenesis of oral submucous fibrosis-a collagen metabolic disorder. J Oral

Pathol Med 2005;34:321-8.
57. Smitha B, Donoghue M. Clinical and histopathological evaluation of collagen fiber orientation in patients with oral submucous fibrosis. J Oral Maxillofac Pathol 2011;15:154-60.
58. Ganganna K, Shetty P, Shroff SE. Collagen in histologic stages of oral submucous fibrosis: A polarizing microscopic study. J Oral Maxillofac Pathol 2012;16:162-6.
59. Khan I, Pant I, Narra S, Radhesh R, Ranganathan K, Rao SG, *et al.* Epithelial atrophy in oral submucous fibrosis is mediated by copper (II) and arecoline of Areca nut. J Cell Mol Med 2015;19:2397-412.
60. Sharma A, Sahni P, Nayak MT, Singhvi A, Kumar R. Identification of the pattern of copper as an etiological factor in oral submucous fibrosis: A cytological study. J Exp Ther Oncol 2014;10:317-23.
61. Mathew P, Austin RD, Varghese SS, Manojkumar AD. Estimation and comparison of copper content in raw Areca nuts and commercial Areca nut products: Implications in increasing prevalence of oral submucous fibrosis (OSMF). J Clin Diagn Res 2014;8:247-9.
62. Trivedy CR, Warnakulasuriya KA, Peters TJ, Senkus R, Hazarey VK, Johnson NW, *et al.* Raised tissue copper levels in oral submucous fibrosis. J Oral Pathol Med 2000;29:241-8.
63. Timonen H. Copper release from copper-T intrauterine devices. Contraception 1976;14:25-38.
64. 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.
65. Sui C, Lacey A. Asia's Deadly Secret: The Scourge of the Betel Nut. BBC News: BBC; 2015.
66. Strait Times Taiwan's Battle with Betel Nut Addiction an Uphill Task. Taiwan: 2017. Available from: https://www.straitstimes.com/asia/east-asia/taiwans-battle-with-betel-nut-addiction-an-uphill-task. [Last accessed on 2018 Jun 25].