

## Clinico-Pathological Evaluation and Correlation of Stages of Oral Submucous Fibrosis with Different Habits

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### Abstract

**Objective:** Oral Submucous Fibrosis (OSF) is a precancerous condition and is mainly associated with the chewing of areca nut. This study was undertaken to correlate the etiological factors (duration, frequency, style and chewing habit) associated with OSF with clinical grading and histological staging.

**Methodology:** A total of 50 clinically and histopathologically diagnosed cases of OSF were included in the study. Detailed clinical examination of each patient was done; emphasizing on their habit. Clinical grading and histological staging of each case was done and the data was recorded in a prescribed format. Statistical analysis was done using chi-square test. Result and observation: A total of 50 subjects were studied, with a male to female ratio of 7.3:1 with age range of 20-30 year. Gutkha-chewing habit alone was identified in 46% of subjects and those associated with gutkha and tobacco were 33.3% with a mean  $\pm$  S.D=32  $\pm$  11.51.

**Conclusion:** The widespread habit of chewing gutkha plays a major role in the development of Oral Submucous Fibrosis than any other habit. The duration and frequency of its use and type of areca nut product has effect on the incidence and severity of OSF.

**Keywords:** Chewing habits; Combination habits; Etiological factors; Gutkha; Oral submucous fibrosis

### Introduction

Oral Submucous Fibrosis (OSF), first described in the early 1950s, is a precancerous condition of oral cavity predominantly seen in people of Asian descent [1]. Oral submucous fibrosis was first described by Schwartz [2]. Pindborg defined it as, "an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat" [2].

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. As a result of transmigration of populations, an increasing number of cases are being seen in other countries [3]. Globally, areca nut is among the most common addictions following tobacco, alcohol and caffeine. Its usage is very popular in India, Taiwan and parts of Southern China. Its chronic use contributes significantly to the high incidence of oral cancer in these countries [3]. Malignant transformation rate of OSF was found to be in the range of 0.5-6% [4]. According to long-term follow-up studies the pooled ratio for chewing tobacco and risk of oral cancer was 4.7 (3.1-7.1) and for pan with tobacco and risk of oral cancer was found to be 7.1 (4.5-11.1), which suggests a strong causal link between oral cancer and various forms of smokeless tobacco [5].

Over the past several decades of industrialization human beings are subjected to physical and mental stress and relieving this stress by taking stress-relieving habits such as smoking, alcohol, betel nut chewing, pan chewing, etc. These Different habits and cultural practices time and again have been abusing the oral cavity. In day-to-day clinical practice our dental researchers reported different oral mucosal alterations. OSF is one such pathological condition [3]. Keeping the above points in view the purpose of this study is to correlate the clinical staging and histopathological grading of OSF with different habit and habit variables to assess the severity of disease.

### Materials and Methods

The present prospective study was carried out in the Department of Oral pathology and Microbiology of our institute. The study subjects were obtained from the outpatient Department of Oral Medicine and Radiology from 2011-2013 after obtaining clearance from the institutional ethical committee. The study group consisted of subjects who were clinically and histopathologically diagnosed as OSF. The subjects who were suffering from any other systemic disease or taking any treatment for OSF or presented with any other oral mucosal lesion, were excluded from the study. Detailed information of each patient regarding the name, age, gender, dietary habits and personal habits were recorded in a pretested proforma. The main emphasis was given on the effect of frequency, duration, manner of chewing (like spitting, swallowing) and different tissue abusive habits (like chewing panmasala, gutkha, plain tobacco, mawa, smoking, and alcohol) on the incidence and severity of OSF. After the detailed clinical examination each patient was categorized as per the criteria described by Bailoor DN (2005) [6]. Incisional biopsy was performed with informed consent

for each patient included in the study to carry out the histopathological diagnosis and the results were recorded according to the grading done by Pindborg and Sirsat [7], who had described four consecutive stages. After obtaining clinical and histological records, all the cases were correlated with the etiological factors, on the clinical as well as histopathological basis. Finally all findings were evaluated and compared, to assess the outcome of the severity of the disease with different habits and habit variables. The data so gathered was sorted, tabulated and subjected to statistical analysis followed by chi-square test. Data analysis and database management were done using SPSS (Statistical Package for Social Science) V16.0.

### Results and Observation

A total of 50 subjects were studied, of which 44(88%) were male and 06 (12%) were female with a male to female ratio of 7.3:1. The maximum number of patients 22 (44%) were in the 20-30 year of age group with a mean  $\pm$  S.D=32  $\pm$  11.51. On the basis of distribution of habit, maximum 39(78%) patients were in the chewing group and 11(22%) were found in the combination group.

According to their personal habit, majority 18 (46.10%) were found with the gutkha chewing habit, 13(33.3%) chewed gutkha with tobacco, 4 (10.20%) patients consumed mainpuri tobacco, 3(7.69%) patients were habituated to pan, 7 (63.6%) patients were addicted to chewing and smoking, 4(36.3%) patients were habituated to alcohol and chewing (Table 1).

Personal habits		No. of patients	Total
Chewing	Gutkha + tobacco (khaini)	13 (33.3%)	39(78%)
	Mainpuri tobacco	04 (10.20%)	
	Gutkha	18 (46.10%)	
	Pan(betaal quid)	03 (7.69%)	
	Plain pan masala	01 (2.56%)	
Combination	Chewing + smoking	07 (63.6%)	11(22%)
	Alcohol + chewing	04 (36.3%)	
Others	Only alcohol	None	-
	Only smoking	None	
Total			50

Table 1: Distribution of patients on the basis of their present habits.

On correlating clinical findings with the patients addiction habits, 13 (26%) patients had OSF grade I, of which 2 (15.3 %) chewed gutkha only, 5 (38.4%) chewed gutkha with tobacco, 1 took manipuri tobacco, 1 took betal quid, 3(23%) were both chewers and smokers, while 1 was addicted to alcohol and chewing. In OSF grade II category, out of 22 (44%) patients, maximum 9 (40.9%) chewed gutkha only followed by gutkha with tobacco. 15 (30%) patients had grade III disease, and of these (46 %) patients consumed only gutkha (Table 2.1).

Habits		Grades			P value
		I	II	III	
Chewing	Gutkha	2(15.3%)	9(40.9%)	7(46%)	P $\geq$ 0.05
	Gutkha +tobacco	5(38.4%)	6(27%)	2(13%)	
	Mainpuri tobacco	1(7.6%)	3(13.6%)	-	
	Pan( betal quid)	1(7.6%)	1(4.5%)	16%	
	Plain pan masala	-	-	1(6%)	
Combination	Chewing+smoking	3(23%)	2(9%)	2(13%)	P $\geq$ 0.05
	Alcohol +chewing	1(7.6%)	1(4.5%)	2(13%)	
Total	50	13(26%)	22(44%)	15(30%)	

Table 2.1: Clinical staging versus habit.

The various etiological factors showed no significant correlation with gradation clinically (Figure 1, Table 2.2). On correlating the histopathological findings with the patients' addiction habits, majority 31 (62%) and 12 (24%) of the patients were found in grade II and III respectively (Figures 3 and 4), of which majority 12(38%) chewed gutkha exclusively. Only 3(6%) and 4(8%) were in OSF grade I and IV respectively (Figures 2 and 5, Table 3.1).

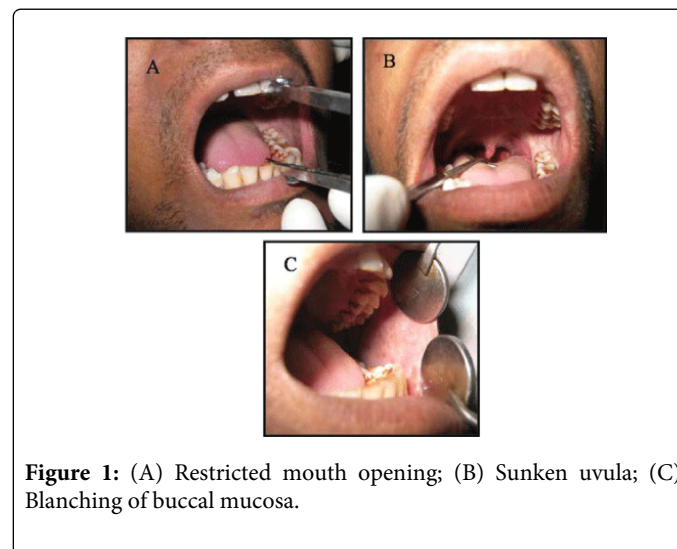
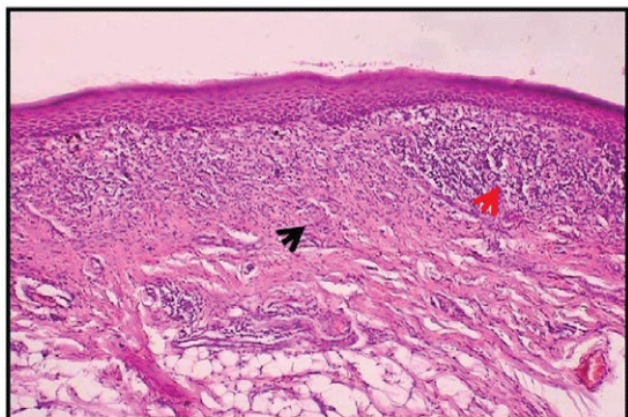


Figure 1: (A) Restricted mouth opening; (B) Sunken uvula; (C) Blanching of buccal mucosa.

Habits	Grades				P value
	I	II	III	Total	
Gutkha only	2(11.1%)	9(50%)	7(39%)	18(36%)	P=.1146; $\chi^2= 4.33$ d. f= 2
Gutkha +others	6(35%)	7(41%)	4(23%)	17(34%)	P=.6625; $\chi^2= 0.824$ d. f=2
Mainpuri tobacco	1(25%)	3(75%)	-	4(8%)	P > 0.05
Combinations	4(36%)	3(27%)	4(36%)	11(22%)	P=.9131; $\chi^2= 0.182$ d. f=2

Table 2.2: Effect of etiological factors on clinical gradation.



**Figure 2:** OSF GRADE I-VERY EARLY STAGE (H&E X100): The black arrow showing fine fibrillar collagen with strong fibroblastic response, red arrow viewing inflammatory cells predominantly polymorphonuclear neutrophils.

Habits		Grades				P value
		I	II	III	IV	
Chewing	Gutkha	1(33%)	12(38%)	3(25%)	2(50%)	
Combination	Gutkha +tobacco	2(66%)	7(22%)	4(33%)	-	P ≥ 0.05
	Mainpuri tobacco	-	4(12.9%)	-	-	
	Pan(beta l quid)	-	2(6.45%)	1(8.33%)	-	
	Plain panmasala	-	-	1(8.33%)	-	P ≥ 0.05
	Chewing + smoking	-	5(16%)	1(8.33%)	1(25%)	
	Alcohol+ chewing	-	1(3.2%)	2(16.6%)	1(25%)	
Total	50	3(6%)	31(62%)	12(24%)	4(8%)	

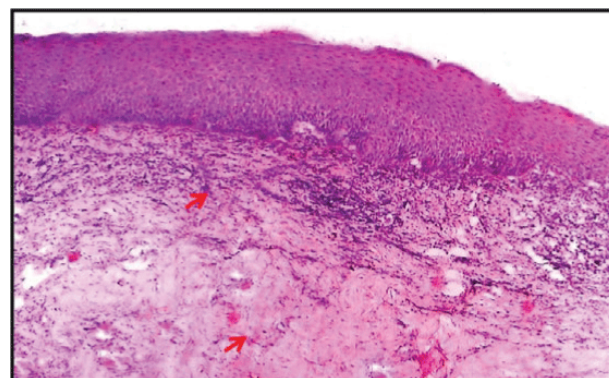
**Table 3.1:** Histopathological grading versus habit.

The etiological factor of gutkha chewing showed significant relation with gradation ( $p > 0.05$  when correlated histologically (Table 3.2)).

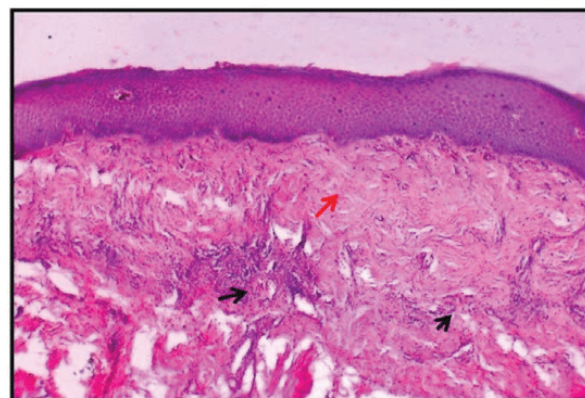
The gender, the age group distribution for OSF grading showed a non-significant variation, whereas the manner of chewing, duration, frequency and time of chewing of the habit showed a significant variation of the clinical as well as histological grading. On statistical analysis, duration of consuming habits showed no significant relation ( $p > 0.05$ ) but the frequency of habits showed significant relation ( $p < 0.05$ ) with consumers who consumed more than 10 packets in a day resulted in increased severity of disease (Table 4). Manner of chewing showed a significant variation when correlated clinicopathologically (Table 5).

Habits	Grades					P value
	I	II	III	IV	Total	
Gutkha only	1(5.5%)	12(66.6%)	3(16.6%)	2(11.1%)	18(36%)	P= .0007; $\chi^2=17.111$ d. f=3
Gutkha+ others	2(11.7%)	9(52.1%)	6(35.2%)	-	17(34%)	P= .1134; $\chi^2= 4.353$ d. f=2
Manipuri tobacco	-	4	-	-	4(8%)	P ≥ 0.05
Combination	-	6(54%)	3(27.2%)	2(18.1%)	11(22%)	P= .3067; $\chi^2= 2.364$ d. f=2

**Table 3.2:** Effect of etiological factors on histopathological gradation.

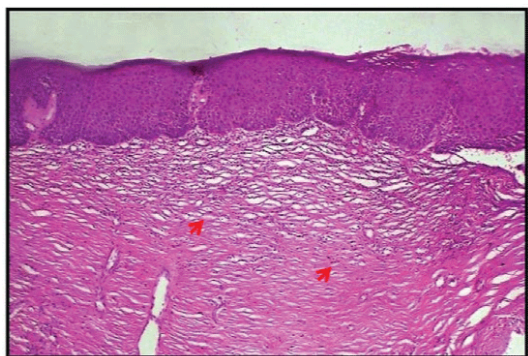


**Figure 3:** OSF GRADE II- EARLY STAGE (H&E X100): The arrowhead showing plump young fibroblasts present in moderate numbers. The blood vessels are dilated and congested. The inflammatory cells are mostly mononuclear lymphocytes.



**Figure 4:** OSF GRADE III- MODERATELY ADVANCED STAGE (H&E X100): The red arrowhead viewing moderately hyalinized Collagen. The black arrow show less fibroblastic response, normal or constricted blood vessels.





**Figure 5:** OSF GRADE IV- ADVANCED STAGE (H&E X100): The arrowhead viewing completely hyalinised collagen, which is devoid of fibroblasts.

### Discussion

Oral submucous fibrosis (OSF) is a chronic and potentially malignant condition of the oral cavity [8]. It is characterized by a juxtaepithelial inflammatory reaction followed by progressive fibrosis of the lamina propria and the underlying submucosal layer, with associated epithelial atrophy and is particularly associated with arecanut and tobacco chewing products [2,9].

The etiopathogenesis of OSF is still obscure, but the causative agent is almost exclusively established as arecanut. It is logical to hypothesize that the increased collagen synthesis or reduced collagen degradation is the possible mechanism in the development of the disease [10-13]. Areca nut (usually incorporated in betel quid) is the fourth most common psychoactive substance in the world (after caffeine, alcohol and nicotine), its use extending to several hundred million people. It has been estimated that betel quid is used by about 10–20% of the world’s population and that globally up to 600 million users chew areca nut [3].

Duration (year)	Clinical stage			P value	Histological stage				P value
	I	II	III		I	II	III	IV	
<10	9	13	8	P = .2634; $\chi^2 = 5.241$ ; d.f= 4	2	20	6	2	P = .8818; $\chi^2 = 2.379$ ; d.f= 6
Oct-20	4	9	5		1	9	6	2	
>20	-	-	2		-	1	1	-	
Frequency (Packets/day)	I	II	III	P ≤ 0.05; $\chi^2 = 43.736$ ; d.f= 6	I	II	III	IV	P ≤ 0.05; $\chi^2 = 63.988$ ; d.f=9
<5/day	9	1	-		-	5	-	-	
>5 <10 /day	4	-	1		3	-	1	-	
>10 <20/day	-	21	13		-	25	12	2	
>20 /day	-	-	1		-	-	-	2	

**Table 4:** Distribution of patients according to duration and frequency of habits (in years).

Style of chewing	I	II	III	P value (clinical)	I	II	III	IV	P value (histological)
2- 5 min	6	3	3	P = .0127; $\chi^2 = 16.208$ ; d.f= 6	-	4	4	1	P = .001; $\chi^2 = 27.903$ ; d.f=9
5-10 min	3	13	5		1	17	8	-	
>10 min	3	6	7		1	10	-	3	

**Table 5:** Distribution of patients according to style of chewing.

In the present prospective study there were 50 subjects (44 males and 6 females) with a male to female ratio of 7.3:1 which shows very strong male predilection. Although OSF affects both sexes, but male predominance for this condition has been noted in many studies [3]. Literature survey of the gender distribution has shown wide variations in the occurrence of OSF. Some epidemiological surveys in India have shown a female predominance [14,15].

Over the years there is a change in the sex predilection of the disease with more and more men falling prey to this condition. Pandey, et al. [13] reported the same result with a male to female ratio of 6.8:1. The male predominance in the present study can be due to easy accessibility for males to use areca nut and its products more frequently than females in our society and changing lifestyle of the youngsters.

The age of individual in the present study ranged from 14 to 65 years. The mean age of the patients was  $32 \pm 11.51$  years. The majority of patients (44%) were lying in the age group of 20-30 years which is similar to other hospital based study [3,16,17]. The age range in patients with OSF is wide and regional. Most of the authors have reported OSF in the age group of 30-40 years while recently some authors categorized it in the age group of 10-29 years [14,18].

In the present study the age and gender distribution in different clinical staging and histopathological grading of OSF showed a non significant findings ( $p > 0.05$ ) suggesting that disease can occur at any age and in any sex in different stages.

In this study according to their personal habits, both the groups (chewer and combination) were found with the habit of chewing tobacco products containing areca nut either in combination or alone of which majority of the patients were found in the chewing group maximally with the habit of gutkha chewing alone, suggesting that chewing tobacco products as compared to combination of habits found to be a major risk factor for developing OSF. It can also be suggested that among various habits, the habit of chewing gutkha exclusively is more prevailing for developing the disease in higher incidence than any other habit; the same finding was appreciated by Reddy et al. [2]. Many authors reported that gutkha and other areca nut product users like mawa, tobacco compared to plain pan masala users showed a significant occurrence of the disease in the severity of the condition [3,19,20].

The reason attributed to the fact that the commercially available freeze dried products such as gutkha, mawa, panmasala etc have higher dry weight concentrations of pathology causing irritants in comparison to the self prepared conventional betel quid that contain smaller amounts of areca nut. Habitual gutka usage is associated with severe oral mucosal disorders, and the consequences may extend beyond the oral cavity [2,21-23]. Kumar et al. reported the pan masala and raw areca nut chewing practices in 81% of the patients who were diagnosed with OSF [13]. While some authors reported the widespread habit of chewing dohra/pan masala is a major risk factor of OSF, especially in the younger age group [13].

In the present study it was found that smoking and alcohol consumption alone have no effect in the development of OSF, but their consumption in the combination along with chewing habits (tobacco products) seen in 22% of patients which found to be a risk factors for developing the disease. In literature it was reported that smoking and alcohol alone have been found to have no correlation with OSF, but their addition to arecanut can act as a risk factor [13]. Similarly Auluck et al. reported that smoking, alcohol drinking along with chewing showed significant association with OSF, leukoplakia and verrucous lesions [24].

On correlating clinical findings with the patient's addiction habit, gutkha chewers showed more preponderance of grade II and III OSF clinically. Similar results were reported in the study done by Reichart and Gupta [19,20]. When compared histologically gutkha chewing showed predominance with grade II and IV. This inconsistency in grade III may be due to limited number of patient in the study. The effect of other concurrent habits like alcohol, smoking, combination habit does not affect the incidence and severity of OSF, which verify that people having areca nut in the form of gutkha shows higher severity and faster occurrence of OSF than any other habit.

In this study etiological factors including type of habits, showed no correlation with gradation clinically, but when compared histologically a significant correlation ( $p < 0.05$ ) was found between etiological factors of gutkha chewing exclusively with gradation, as compared to any other habit. Reddy et al. in their study compared gutkha, arecanut, tobacco, and mawa chewers which showed a significant occurrence of OSF in severity of condition clinically [2].

The habit variables in the form of frequency and manner of chewing showed statistically significant relation with the severity of clinical and histological grading while duration of consuming habit showed no significant relation with the severity of disease. Subjects who chewed for more than 10 packets per day and kept in mouth for more than 5 minutes each packet showed the highest rate of occurrence. This is in accordance to literature which explains that tobacco products containing arecanut has high alkaloid, arecoline and tobacco ingredients like nitrosamine, which are absorbed more in the patients who keep it for longer duration and swallow it [1,2,25,26]. On the contrary, Ali et al. suggested that severity of OSF depends on duration and frequency of habit [3].

The occurrence of OSF was seen significantly in those having one or the other forms of areca nut which showed that the product which leaches out from areca nut would be responsible for the development of OSF [1,27]. People having tobacco alone have never been seen to have OSF. This was also observed in our study that there was no synergistic effect of any habit in the development of OSF. If tobacco would have been a causative factor for OSF then other forms of tobacco like cigarette, bidi, pipe smoking should have manifested OSF as one of the clinical feature. In the areca nut chewers the Lysyl oxidase activity is unregulated to alter fibroblast metabolism producing more collagen. This may add to the conclusion of the occurrence of OSF due to the products leaching out from areca nut causes OSF and not from those leaching out from tobacco [1,27].

Although OSF is a progressive disease and it spreads even after stopping the habit. Treatment of OSF includes various modalities but the main step to avoid progression of the disease is to stop the habit completely. The habit of chewing tobacco products is increasing because of its legality, free and easy availability. Relatively cheap cost and promotions of these areca nut products especially gutkha and pan masala outside the schools, colleges and social places has impacted younger population in India, which led to the increased episodes of premalignant condition and malignancies in these age groups. Now, it is time we should stopped making this artificial distinction between these tobacco products and definitely we must take strong and sturdy step for the cessation of such habits by conducting some awareness programs.

## Conclusion

The widespread habit of chewing gutkha has major role in the occurrence and severity of OSF, especially in younger age group. The occurrence of OSF in gutkha chewers is faster and more severe as compared to any other forms of areca nut products. The relative risk of disease increased with frequency and manner of chewing which conclude that the daily consumption rate appears to be relatively significant with respect to risk than the lifelong duration of habit. The histological grade should be considered as the gold standard in deciding the treatment plan and routine surveillance programmes should be carried out in order to stop these perilous habit.

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