



ISSN NO. 2320-5407

Journal homepage: <http://www.journalijar.com>  
Journal DOI: [10.21474/IJAR01](https://doi.org/10.21474/IJAR01)

INTERNATIONAL JOURNAL  
OF ADVANCED RESEARCH

## RESEARCH ARTICLE

## Liver fibrosis in OSMF patients and areca nut chewers: an ultrasonographic study.

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## Manuscript Info

## Manuscript History:

Received: 18 March 2016  
Final Accepted: 29 April 2016  
Published Online: May 2016

## Key words:

Liver fibrosis, ultrasound, arecoline, oral submucous fibrosis.

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## Abstract

**Aim & Objective:** Prolonged areca-nut chewing, apart from causing oral submucous fibrosis, has also been reported to cause various systemic ill effects including fibrosis of visceral organs like liver, pancreas and gall bladder. Other than animal studies, such evidences have also been obtained from population based observational studies. To gain further insight, this study was conducted to test a hypothesis that prolonged areca-nut chewing may lead to liver fibrosis.

**Material and Method:** Thirteen prolonged areca nut chewers with OSMF (*Study group-1*), eight prolonged areca-nut chewers without OSMF (*Study Group-2*) and five healthy individuals without deleterious habits (*Control Group*) were subjected to ultrasonographic study of abdomen.

**Result:** 19% of total study subjects and none in control showed fibrotic changes in liver. Out of which 75% were OSMF patients and 25% were areca nut chewers without OSMF.

**Conclusion:** Ill effects of areca nut chewing may be evident in liver even before it involves the oral mucosa without the effect of other risk factors.

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## Introduction:-

Areca-nut is the fourth most commonly chewed addictive substance and is known to produce mutagenic and genotoxic effects in body tissues. It is widely consumed in Asian countries, primarily the Indian subcontinent and is considered one of the primary causes of submucous fibrosis (OSMF) especially in genetically predisposed individuals.<sup>[1]</sup> It has been reported that the ill effects of areca nut chewing are not only confined to the oral mucosa, but also to various systemic organs like pancreas, liver and gall bladder. Additionally, systemic effects like diabetes mellitus, thyroid dysfunction, central obesity, peptic ulceration, liver fibrosis, conductive hearing loss, hematinic disturbances, cachexia and malnutrition have been documented.<sup>[2-5]</sup>

OSMF is predominantly seen in the Indian subcontinent and it's emigrants to other parts of world.<sup>[6]</sup> It affects about 0.2 to 0.5% of Indian population, with slight male predilection and is most commonly seen in age group of 16 to 35 years, though it can occur at any age.<sup>[7]</sup>

Recently an exponential increase in the disease incidence has been noted in India, probably due to the upsurge, in the popularity of commercially prepared paan masala and gutkha among the younger generation.<sup>[7]</sup>

Oral sub-mucous fibrosis is a chronic insidious disease characterised by progressive irreversible fibrosis of the oral and pharyngeal mucosae, primarily, directly exposed to areca alkaloids.<sup>[8]</sup> However as discussed above, there are evidences that these fibrotic changes are not confined only to the mucosa in direct contact with the areca-nut.<sup>[9]</sup> In vivo studies have reported increased serum aminotransferase level with hepatocellular damage in CD1 mice, fed with areca nut.<sup>[10]</sup> Rajendran R et al reported hyperechoic areas in liver parenchyma suggesting “fibrosis”, in 24% of the OSMF patients who were evaluated ultrasonographically. However, this study failed to rule out the influence of alcohol, if any, in these patients.<sup>[11]</sup> Unexplained hepatocellular damage has been reported as an unusual common problem in East London Bangladeshi’s, who are habitual chronic areca nut chewers but non-alcoholics.<sup>[2]</sup>

Hence, a hypothesis was proposed that “prolonged areca-nut chewing may cause fibrotic changes in liver parenchyma” and in a case control study individuals with long term areca nut chewing habits with or without concurrent OSMF were evaluated for evidence of fibrosis in liver using ultrasonography.

### Materials and methods:-

This pilot study was carried out in the Department of Oral Medicine and Radiology, People’s College of Dental Sciences and Research Centre, Bhopal for a period of two weeks, in July 2015 among 26 individuals of either sex in the age group 14- 45 years (Table 1). Prior ethical approval was obtained from the Institutional Ethical Committee. The study subjects were divided, under three groups. *Study group 1* comprised of 13 otherwise systemically healthy OSMF patients of Grade III and Grade IV A, having prolonged areca nut chewing habit. The *Study group 2* comprised of 8 individuals with prolonged (> 5 years) areca nut chewing habit without any clinical evidence of OSMF and *Control group* comprised of 5 healthy individuals without any deleterious habits or evidence of OSMF. The exclusion criteria included individuals above 45 years, those who gave history of alcohol consumption and any systemic disease which may interfere with the study protocol. Older individuals were excluded as they would be susceptible to physiologic fibrotic changes in liver.

OSMF was diagnosed and graded according to the *Khanna JN and Andrade NN et al, (1995)* criteria.<sup>[7]</sup>

After obtaining detailed history, clinical examination and written informed consent, each individual was subjected to ultrasonographic examination of the abdomen, to assess for any evidence of hyperechoic areas suggestive of fibrotic changes in the liver parenchyma.

The data so obtained was then tabulated and statistically analysed using Chi square test and Pearson’s coefficient.

### Results:-

Out of 26 individuals examined, evidence of hyperechoic areas suggesting fibrotic changes in liver was observed among **23%** (n=3/13) of OSMF patients out of which **15%** (n=2/13) were having Grade IV and **7%** (n=1/13) had Grade III OSMF. Similarly **12.5%** (n=1/8) of prolonged areca-nut chewers without OSMF showed few hyperechoic areas in liver parenchyma. [Table 2 and Table 3].

Even though the result was statistically non significant (p=0.460) these alarming changes warrant a definite mention. Liver fibrosis was observed more among Grade IV OSMF than Grade III OSMF individuals [Table 2].

**Table1: Age and sex distribution of OSMF patients, areca-nut chewers and controls.**

Age (in years)	Study Group 1 (OSMF patients)			Study Group 2 (Areca-nut chewers)			Control (Healthy individuals)		
	Males (n=10)	Females (n=3)	Total (n=13)	Males (n=5)	Females (n=3)	Total (n=5)	Males (n=3)	Females (n=2)	Total (n=5)
<b>Range</b>	15-39	30-40	15-40	14-40	22-36	14-40	17-24	21-42	20-42
<b>Mean Age</b>	22.8	36.7	<b>26</b>	32.2	31	<b>31.75</b>	20.3	31.5	<b>24.8</b>

**Table 2: Distribution of patients with liver fibrosis**

Groups	Liver fibrosis		P value
	Present	Absent	
<b>OSMF patients</b>	3	10	P>0.05
<b>Areca nut chewers</b>	1	7	
<b>Controls</b>	0	5	

**Table 3: Distribution of OSMF grade III and IV among OSMF patients**

OSMF patients	Liver fibrosis		P value
	Present	Absent	
OSMF Grade III	1	6	p>0.05
OSMF Grade IV	2	4	

### Discussion:-

Areca nut is commonly used as a psychoactive addictive substance. There is a strong belief among people who consume areca nut that it aids in digestion and acts as a stimulant<sup>1</sup>. It plays a vital role in the pathogenesis of oral mucosal lesions like submucous fibrosis. Other systemic ill effects include obesity, diabetes, fibrosis of tubular and paratubular muscles leading to eustachian tube dysfunction and conductive hearing loss, debilitating condition like cachexia, and decreased haemoglobin and iron serum level.<sup>2-5</sup> In vivo studies, in animal models have reported that areca fed rats developed diabetes after prolonged consumption. Even the non fed offspring of areca fed fathers developed diabetes at a greater rate when compared to non fed offspring of areca fed mothers.<sup>7</sup> Extensive research is being carried out to unravel the systemic and local ill effects of areca nut chewing.

Alkaloids of arecanut, primarily arecacoline, mostly target oral fibroblasts and myofibroblasts cells. Myofibroblast acts as a primary collagen producing cell that results in submucosal fibrosis. Abnormal collagen metabolism leads to fibrosis of the submucosal tissues in the areas exposed to arecanut, primarily oral mucosa. Increased deposition of  $\alpha$ -Smooth Muscle Actin ( $\alpha$ -SMA) myofibroblasts is also evidenced in the biopsy specimens of OSMF which are also the marker of progressive fibrosis of organs like liver, kidney, lungs and skin.<sup>12</sup>

Areca-nut has shown to have a high copper content that leaches into saliva and gets circulated in the oral cavity. Copper dependant lysyl oxidase enzyme upregulates the cross-linkage of collagen and elastin fibres that causes fibrosis of submucosal tissues.<sup>13</sup> Fibrotic diseases like liver cirrhosis and scleroderma, also have shown, increased level of copper, as reported by Trivedy C et al, 1997. Thus, it may be hypothesised, that high copper content of areca nut can have an effect on internal organs leading to fibrosis.<sup>14</sup>

Cirrhosis of the liver has been found to be an unusually common problem in regular areca nut chewers in East London Muslim immigrants though it may be occasionally accounted for by chronic viral hepatitis B and rarely by the use of alcohol.<sup>2</sup>

In the present study, we found fibrotic changes in 23% of OSMF patients and 12.5% of the areca-nut chewers and none in healthy individuals. Fibrotic changes in liver increased with the severity of OSMF, evident in 33.3% of total Grade IV A OSMF patients and 14.2% of total Grade III OSMF patients. The result was statistically non-significant (p=0.460) probably because of small sample size. It is noteworthy; however, that arecanut chewing can lead to fibrosis of liver. For significant results, a larger sample size and better investigation modalities are advocated.

Various theories have been put forth explaining fibrotic changes in visceral organs like liver. In vivo studies in animal models have reported that prolonged areca nut chewing leads to increase in serum aminotransferases level that results in abnormal liver function.<sup>2</sup>

It has been studied that daily quid chewing (among East london Bangladeshis) may lead to increase in plasma Tissue Inhibitor Metalloproteinases -1 concentration that contribute to the risk of disorders like cirrhosis of liver and hypertensive ventricular hypertrophy.<sup>2</sup>

In our study, the results corroborate the hypothesis that prolonged areca nut chewing may lead to fibrosis of liver. We have evidenced a significant finding that areca nut consumption can cause fibrotic changes in liver even before the appearance of oral abnormalities like submucous fibrosis.

To best of our knowledge, this is a pioneering study assessing liver fibrosis in prolonged arecanut chewers with or without concurrent OSMF, which could be corroborated with a larger sample size. This could prove a vital instrument in ridding the community of this addictive substance abuse.

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