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# Serum Copper and Iron Levels in Relation to the Clinical stages of Oral Submucous Fibrosis

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**Abstract**

Oral submucous fibrosis (OSMF) is a chronic disease of the oral cavity, which is characterized by an epithelial and sub epithelial inflammatory reaction followed by fibro elastic changes in the submucosa. To estimate the levels of serum copper and iron among subjects with OSMF of different clinical stages and healthy controls. Study sample comprised of 40 patients clinically diagnosed with OSMF and 40 healthy controls who were matched for age and gender. OSMF patients were categorised by clinical staging. Serum estimation of copper and iron were done using atomic absorbtion spectrophotometry. Mean copper and iron level differed significantly ($p<0.000$) between the patients and controls with patients exhibiting higher copper and lower iron levels in contrast to controls who presented lower copper and higher iron levels in serum. Copper levels were found to increase while iron levels decreased in the study group, corresponding with the advancement of clinical stages in OSMF.

**Keywords:** Oral Submucous Fibrosis, Serum Iron, Serum Copper, Clinical Staging, Subepithelial Inflammation.

## Introduction

Oral submucous fibrosis (OSMF) is a long-lasting, precancerous ailment that predominantly affects individuals from South and Southeast Asia, particularly those of the Indian subcontinent [1-7]. This disease has now become an epidemic in India, affecting approximately 2.5 million individuals [8-9]. OSMF is a long-term, gradual, and debilitating disorder of the oral mucosa, marked by epithelial atrophy and a progressive buildup of collagen fibers in the lamina propria and submucosa [10]. OSMF is a well-recognized, potentially premalignant condition. Reports from the Indian subcontinent indicate a malignant transformation rate reaching 7.6% over a span of 17 years. 8, 10-16Younger generations are most commonly noted to have OSMF cases due to the use of smokeless tobacco products. Smokeless tobacco refers to any type of tobacco product that is used in ways other than smoking. Nonetheless, smokeless tobacco contains a number of carcinogens, including nicotine, tobacco-specific N-nitrosamines, arsenic, beryllium, chromium, nitrite, nitrate, cadmium, nickel, and the polynuclear hydrocarbon benzo[a] pyrene [11]. These carcinogenic substances induce dysplastic alterations in the oral mucosa and result in a variety of pathological lesions [11]. It has been proposed that areca nut chewing, chilli consumption, genetic predisposition, nutritional deficiencies, autoimmunity, and collagen disorders may play a role in the development of this condition. The etiology most often regarded as responsible for OSMF is—are coline, a component of areca nut[12-14] Gutkha is recognized for containing various trace elements, such as copper (Cu), zinc (Zn), selenium (Se), and molybdenum (Mo). Hence, it might affect the serum and salivary concentrations of trace elements [15]. The present study aimed to estimate the levels of serum Cu and Fe trace elements in patients with OSMF, as gutkha intake is one of the factors responsible for OSMF and contains several trace elements that can influence the levels of trace elements in the consumer's body [16]. In the initial cases of OSMF, the oral mucosa develops a blanched and slightly opaque appearance[17-19]. In advanced instances of OSMF, mucosal fibrosis manifests, resulting in rigidity primarily affecting the palate, buccal mucosa, and faucial pillars. As fibrosis progresses, opening the mouth becomes difficult, whistling or blowing out a candle is impossible, and swallowing can sometimes pose a challenge [17-18].

## Material and Methods

### Study subjects

This cross sectional study included 40 participants (group A) diagnosed with OSMF, all of cases were visiting and registered at the Chandra Dental College and hospital, Barabanki. Additionally, 40 OSMF free healthy controls (group B) were included for comparison. Cases and controls were matched based on ethnicity, age, and sex to ensure comparability and minimize confounding variables in the analysis. Ethical approval for this study was cleared by the ethical committee of Chandra Dental college & Hospital, Safedabad, Barabanki, (U.P.), India (Reference no: CDCH/EC/OPM/2023-26/025). This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was collected from all participants. Venous blood samples were collected in EDTA and plain tubes, thoroughly mixed, and stored at −80 °C for future analysis.

### Methods

All the details of patients like name, age, sex, occupation and address were recorded. A detailed history of OSMF patients (figure 1) consisting of chief complaint, past and present illness, and medical history were recorded. Emphasis was made on recording any oral habit of chewing areca nut, paan (betal quid), gutka, smoking bidi

or cigarette along with duration and frequency of habit per day. About 5ml of venous blood was drawn intravenously and sample was centrifuged at 1000-1500 RPM for 15 minutes at room temperature.

Subsequently 2ml of serum was pipetted out and analysed for copper and iron by atomic absorption spectrometry (AAS). (AAS) is a quantitative analytical technique used to determine the concentration of metallic elements in the sample by measuring the absorption of light by free, gaseous atoms. The method involves atomizing the sample (often with a flameorgraphitefurnace) and then passing a light source with a specific wavelength for the element through the atomizedvapor. The amount of light absorbedisproportional to the concentration of the element in the sample. This absorbance is directly related to the concentration of the element in the sample according to the Beer-Lambert law.

**Statistical analysis**

Mean and standard deviation were calculated for serum copper and iron levels in the study and control subjects. The analysis of the data was conducted utilizing SPSS version 25.0 (IBM Corp., Armonk NY, USA). For continuous variables, we use the mean +/- Standard Deviation (SD) and for categorical variables, we use frequency and percentage. The independent t-test was used to compare the mean serum copper and iron levels between patients with Oral Submucous Fibrosis (OSMF) and healthy controls. A one-way ANOVA was performed to evaluate differences across the various OSMF grades. To identify specific group-level differences, Tukey's post hoc test was subsequently applied.

We used the Chi-Square (X2) test to compare categorical variables like the distribution of gender. A p-Value of less than 0.05 was statistically significant, and p-value of less than 0.001 was very significant.

**Results**

**Characteristic of the study population**

Table 1 shows a detailed demographic and clinical profile of the study participants. The gender distribution indicates that (72) 90% of the participants are male, whilst females constitute (8)10%. The age distribution shows that the majority of participants are in the41-50 years category (40%), followed by those aged 31-40 years (26.25%), 51-60 years (18.75%), and those aged 30 years or younger (15%). The mean age is 42.33 years, with a standard deviation of9.80 years. The habit history is evenly divided, with (40)50% of participants exhibiting a habit (presumably areca nut or tobacco use) and the remaining (40) 50% devoid of any such habit. In a cohort of 40 persons diagnosed with OSMF, the distribution of clinical grades reveals Grade 3 as the predominant classification (62.50%, 25 participants), succeeded by Grade 1 (20%, 8 participants) and Grade 2 (17.50%, 7 participants).

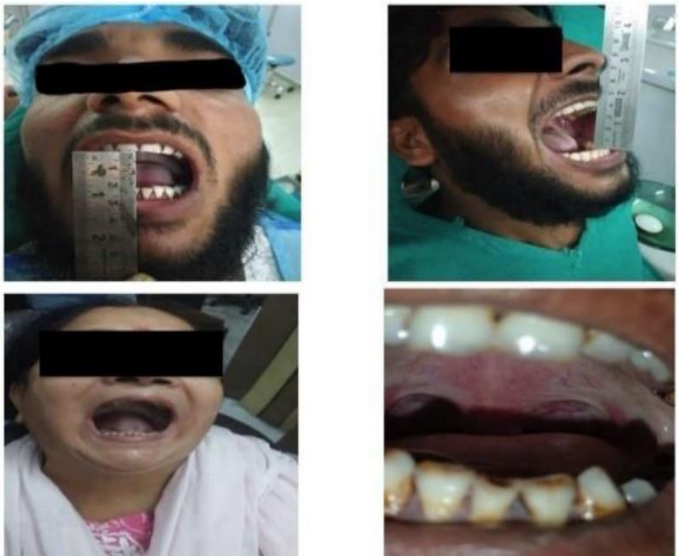


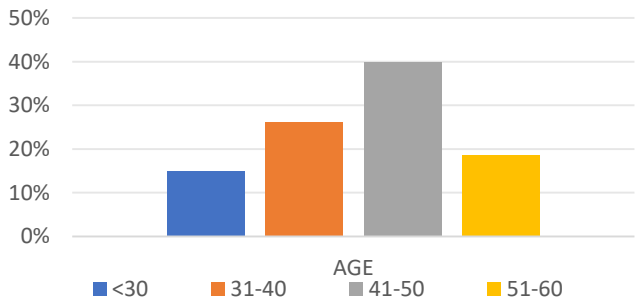
Figure: 1 Patients with symptoms of Oral Submucus Fibrosis

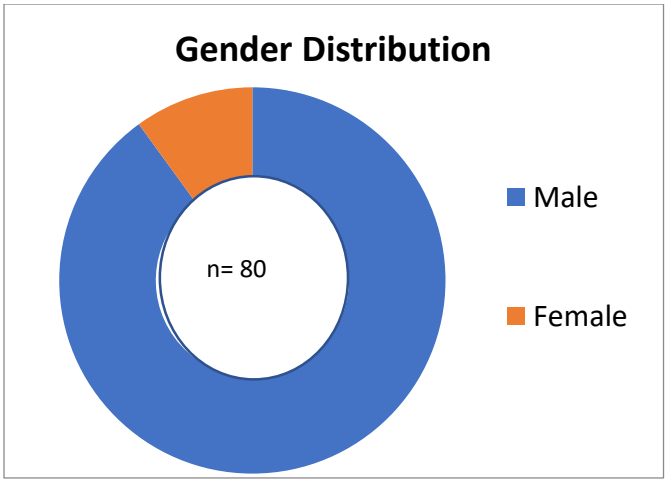
Table 1: Demographic and Clinical Characteristics of Study Participants

| Variables | | n=80 | n=% |
|---|---|---|---|
| Gender | Male | 72 | 90 |
| | Female | 08 | 10 |
| Age | ≤30 years | 12 | 15 |
| | 31-40 years | 21 | 26.25 |
| | 41-50 years | 32 | 40 |
| | 51-60 years | 15 | 18.75 |
| | Mean±SD | 42.33±9.80 | |
| Habit history | Present | 40 | 50 |
| | Absent | 40 | 50 |
| OSMF grade (n=40) | Grade I | 8 | 20 |
| | Grade II | 7 | 17.50 |
| | Grade III | 25 | 62.50 |

Age wise distribution of study participants

Table 2 compares the mean age of Group A (individuals with OSMF) with Group B (healthy controls). The mean ages of both groups are practically identical: 42.35 ± 9.32 years for Group A and 42.30 ± 10.37 years for Group B. The t-test statistic is 0.02 and the p-value is 0.982, signifying no statistically significant difference in age between the two groups.



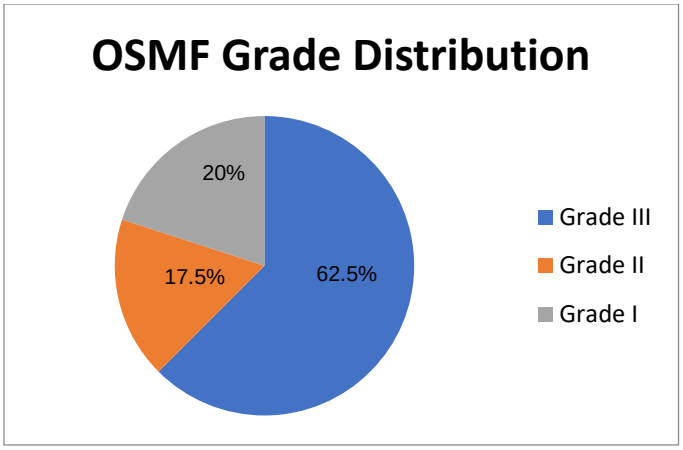




Figure: 2 shows a detailed demographic and clinical profile of the study participants. The gender distribution indicates that 90% of the participants are male, whilst females constitute 10%. The age distribution shows that

the majority of participants are in the 41-50 years category. In a cohort of 40 persons the distribution of clinical grades reveals Grade 3 as the predominant classification (62.50%, 25 participants), succeeded by Grade 1 (20%, 8 participants) and Grade 2 (17.50%, 7 participants).

Table 2: Comparison of Age between Group A (OSMF) and Group B (Controls)

| | Group (n=40) | | Group (n=40) | | T | P-value |
|---|---|---|---|---|---|---|
| | Mean | ±SD | Mean | ±SD | | |
| Age (yrs) | 42.35 | 9.32 | 42.30 | 10.37 | 0.02 | 0.982 |

Age Comparison

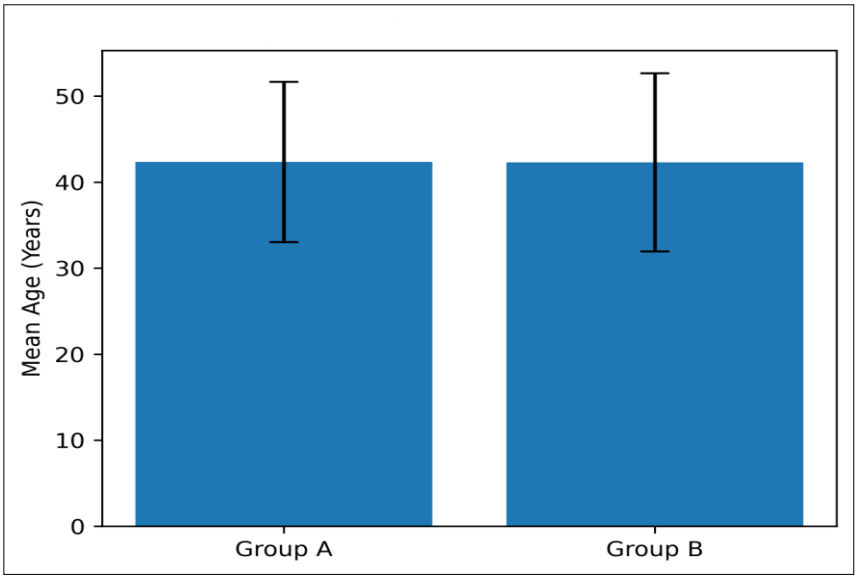



Figure 3: Shows Comparison of Age between Group A (OSMF) and Group B (Controls)\

**Gender distribution among study participants**

The gender distribution of Group A (OSMF patients) and Group B (controls) is presented in Table 3. Each group comprises 90% men (36participants) and 10% women (4 individuals). Both groups were comparable in terms of gender distribution.

Table 3: Gender Distribution in Group A (OSMF) and Group B (Controls)

| Gender | Group A (n=40) | | Group B (n=40) | | Chi Sq | p-Value |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| Male | 36 | 90.00 | 36 | 90.00 | | |
| Female | 4 | 10.00 | 4 | 10.00 | | |
| | | | | | 0.00 | 1.00 |

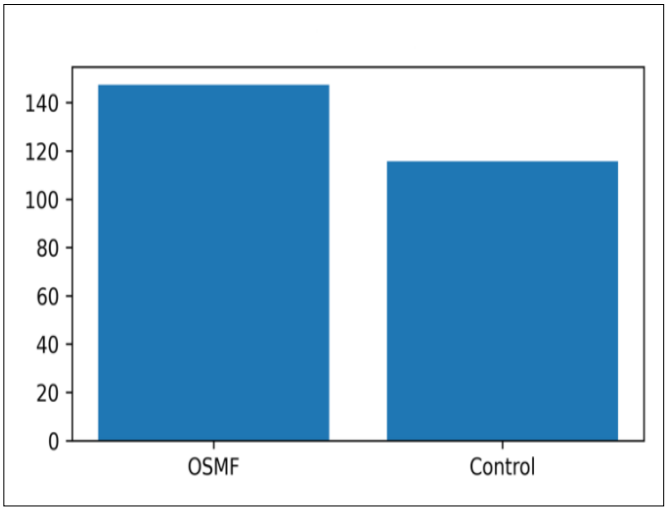
**Comparison of Serum Iron Levels and serum copper levels between Group A and Group B**

Table 4 shows the comparison of mean serum iron levels between Group A (OSMF patients) and Group B (controls). The mean serum iron levels were significantly lower in group A (109.88 ± 10.17) as compared to Group B (129.15 ± 8.94). Table 4 shows the comparison of mean serum copper levels between Group A (OSMF patients) and Group B (controls). The mean serum copper

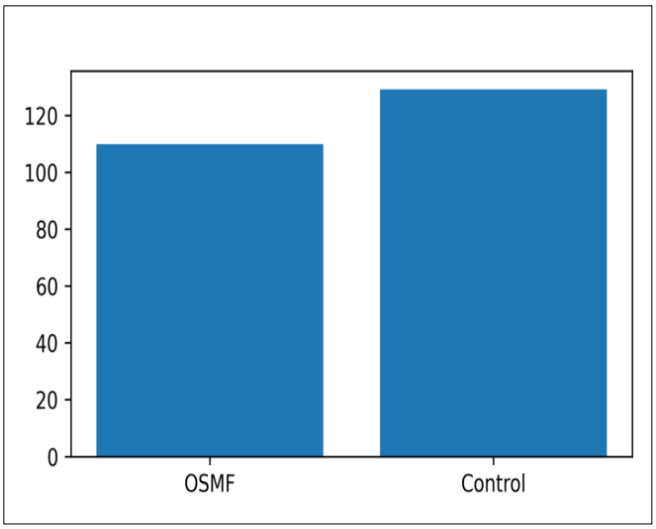
level was significantly higher in Group A (147.42±20.47) compared to Group B (115.79±5.61).

Table 4: Comparison of Serum Iron Levels and serum copper levels between Group A (OSMF) and Group B (Controls)

| | Group A (n=40) | | Group B (n=40) | | T | p-Value |
|---|---|---|---|---|---|---|
| | Mean | ±SD | Mean | ±SD | | |
| Serum Iron level | 109.88 | 10.17 | 129.15 | 8.94 | 18.87 | <0.001 |
| Serum copper level | 147.42 | 20.47 | 115.79 | 5.61 | 9.00 | <0.001 |




Serum Copper




Serum Iron

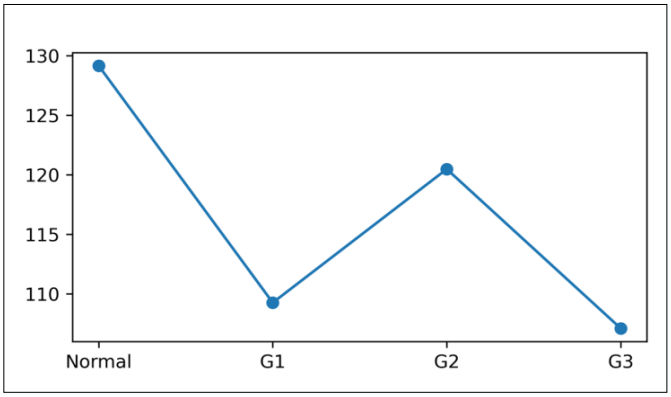
Figure 4: Shows comparison of Serum Iron Levels and serum copper levels between Group A (OSMF) and Group B (Controls)

**Comparison of Mean Serum Iron Levels and mean serum copper level across OSMF Clinical Grades and Normal Controls**

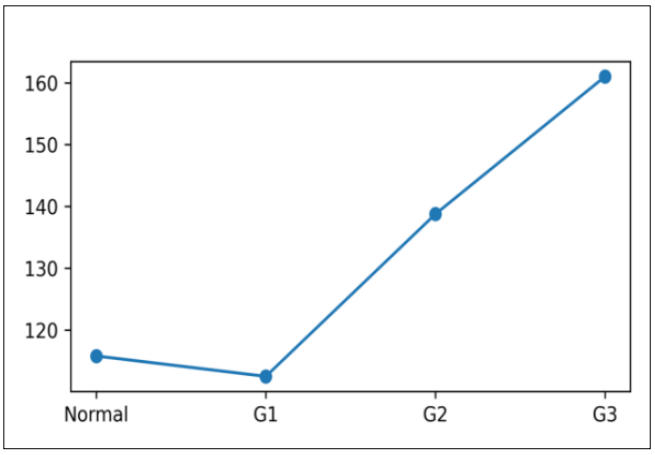
Table 5 shows the comparison of mean serum iron levels among normal controls and different clinical grades of Oral Submucous Fibrosis (OSMF). Normal controls exhibited the highest mean serum iron level (129.15 ± 8.94), while the levels were lower in all OSMF grades. Grade 2 had a mean of 120.48± 15.70, Grade1had109.27±4.95 and Grade 3 showed the lowest mean serum iron level at107.11 ± 7.64. The differences in serum iron levels across these groups were statistically significant (<0.001). The total mean serum iron level for all participants was 119.52 ± 13.58. Mean serum copper levels among normal controls and different clinical grades of Oral Submucous Fibrosis (OSMF). Normal controls had a mean serum copper level of 115.79±5.61. Among OSMF grades, the mean serum copper levels increased progressively with severity: Grade1had112.49±9.53, Grade 2 had 138.76±6.62 and Grade 3 showed the highest level at161.02±4.72. The differences in serum copper levels across these groups were statistically significant with an F-value of 332.60 and a p-value less than 0.001. The overall mean serum copper level for all participants was 131.60 ± 21.81.

Table 5: Mean Serum Iron Levels and serum copper levels across OSMF Clinical Grades and healthy controls

| | | N | Mean | ±SD | F | p-Value |
|---|---|---|---|---|---|---|
| Serum Iron level | Normal controls | 40 | 129.15 | 8.94 | 34.56 | <0.001 |
| | Grade1 | 8 | 109.27 | 4.95 | | |
| | Grade2 | 7 | 120.48 | 15.70 | | |
| | Grade3 | 25 | 107.11 | 7.64 | | |
| | Total | 80 | 119.52 | 13.58 | | |
| Serum copper level | Normal controls | 40 | 115.79 | 5.61 | 332.60 | <0.001 |
| | Grade 1 | 8 | 112.49 | 9.53 | | |
| | Grade 2 | 7 | 138.76 | 6.62 | | |
| | Grade 3 | 25 | 161.02 | 4.72 | | |
| | Total | 80 | 131.60 | 21.81 | | |




Iron




Copper

Figure 5: Shows mean serum Iron Levels and serum copper levels across OSMF Clinical Grades and healthy controls

**Post-hoc Tukey Test for Serum Iron Levels and Post-hoc Analysis of Serum Copper Levels among OSMF Grades and Controls**

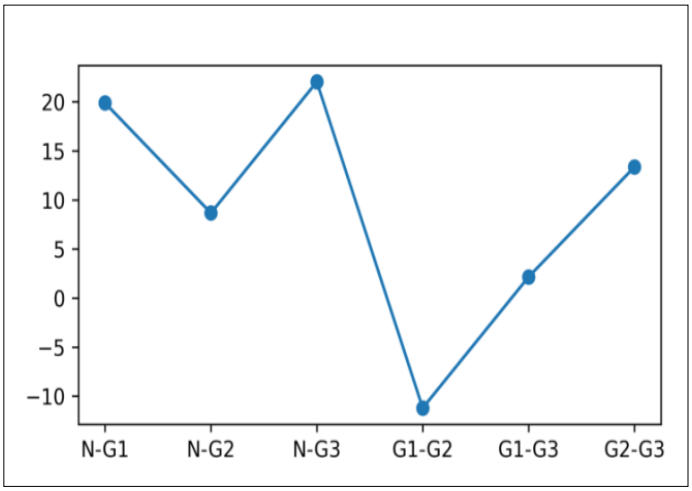
Table 6 presents the post-hoc Tukey test results for serum iron levels among normal controls and different OSMF grades. The mean serum iron level in normal controls was significantly higher than in Grade 1 (mean difference 19.89, $p < 0.001$) and Grade 3 (mean difference 22.05,$p < 0.001$).The difference between normal controls and Grade 2 (mean difference 8.67) was not statistically significant($p=0.096$).AmongtheOSMFgrades,thedifferencebetweenGrade 2 and Grade 3 was significant (mean difference 13.37, $p = 0.005$), while comparisons between Grade1and Grade 2 (mean difference - 11.21, $p = 0.085$) and between Grade 1 and Grade 3 (mean difference 2.16, $p = 0.935$) were not statistically significant.

Post-hoc analysis of serum copper levels among normal controls and different OSMF grades. There was no significant difference in serum copper levels between normal controls and Grade 1 (mean difference 3.30, $p = 0.478$). However, serum copper levels were significantly higher in Grade 2 and Grade 3 compared to normal controls, with mean differences of-22.98and -45.23 respectively (both $p < 0.001$). Significant differences

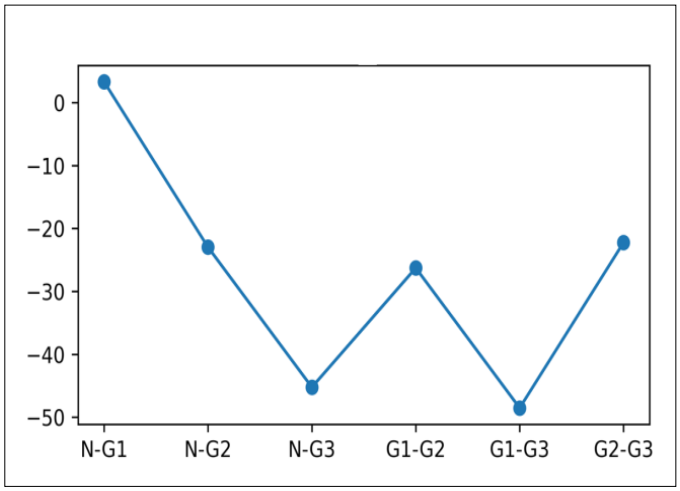
were also found between Grade 1 and Grades 2 and 3, with mean differences of -26.28 and -48.53 respectively (both $p < 0.001$). Additionally, Grade 3 had significantly higher serum copper levels than Grade 2 (mean difference -22.25, $p < 0.001$).

Table 6: Post-hoc Tukey Test for Serum Iron Levels among OSMF Grades and Controls and Post-hoc Analysis of Serum Copper Levels among OSMF Grades and Controls

| Serum Iron level | | Mean Difference | p-Value |
|---|---|---|---|
| Normal controls | Grade1 | 19.89 | <0.001 |
| | Grade2 | 8.67 | 0.096 |
| | Grade3 | 22.05 | <0.001 |
| Grade1 | Grade2 | -11.21 | 0.085 |
| | Grade3 | 2.16 | 0.935 |
| Grade2 | Grade3 | 13.37 | 0.005 |
| Serum copper level | | Mean Difference | p-Value |
| Normal controls | Grade1 | 3.30 | 0.478 |
| | Grade2 | -22.98 | <0.001 |
| | Grade3 | -45.23 | <0.001 |
| Grade 1 | Grade2 | -26.28 | <0.001 |
| | Grade3 | -48.53 | <0.001 |
| Grade 2 | Grade3 | -22.25 | <0.001 |




Iron




Copper

Figure 6: Shows Post-hoc Tukey Test for Serum Iron Levels among OSMF Grades and Controls and Post-hoc Analysis of Serum Copper Levels among OSMF Grades and Controls

**Discussion**

OSMF is a chronic precancerous state predominantly seen in Asian countries marked by epithelial atrophy and a progressive built up of collagen fibers in the lamina propria and submucosa[10]. The graveness can be estimated from the fact that in our country India alone about 2.5 million individuals have some form of clinical findings of OSMF and only minimal percentage of affected individuals seek consultation/ treatment [8-10]. The patients usually become aware only in later stages when the disease becomes irreversible. Reports indicate a malignant transformation rate reaching 7.6% over a span of 17 years [10-16]. The probable culprit behind such humongous increase is the popularity of commercially prepared areca nut and tobacco preparations gutkha, pan masala, mawa, flavoured supari, etc. The use of areca nut is thought to be the most important causative factor [20]. It is concerning how quickly oral malignant and precancerous tumors are spreading like an epidemic. Oral precancerous lesions are far more common than oral cancer, and they serve as helpful clinical indicators for the disease [21]. Chewing areca nuts is currently thought to be the primary cause of OSF [22]. Numerous carcinogens found in tobacco and related products, such as nitrosamines and polynuclear aromatic hydrocarbons, are involved in the etiology of OSCC [23]. The importance of trace elements in human health, whether positive or negative, has become more widely recognized over time. A "trace constituent" is any component whose concentration is equal to or less than 0.01% (100 parts per million) of the entire matrix [24]. Areca nut contains tannins, Gallotannic acid, D Catechol, Alkaloids, Arecoline, arecaidine, guvacine and isoguvacine, arecolidine and guvacoline. Out of all are caidine is an active metabolite in fibroblast stimulation and proliferation, there by inducing collagen synthesis[25]. Gutka contains various trace elements, such as copper (Cu), zinc(Zn), selenium (Se), and molybdenum (Mo) [15]. Since trace elements are crucial for bodily processes, everyday functions and is significant for collagen metabolism. Its estimation can prove beneficial in diseased state[26].

Our findings of low serum iron levels in OSMF as compared to healthy controls was also reported in many previous studies by researchers like Karthik et al (2025), Thakur et al (2017), Jassim et al (2020), Yadav et al (2015) and Keerthana et al (2020) [27,28,29-31].

Iron deficiency in OSMF could make it severe by reducing the body's capacity to heal damaged tissues and manage inflammation.

However, it should be noted that few iron–related markers have been demonstrated to increase in OSMF patients as compared to healthy controls as reported by Wu et al (2021). Increased Total Iron Binding Capacity (TIBC) is also reported in OSMF when compared to controls as per the findings on Jassim et al (2020) [30,32]. It is well established that one of the important components of connective tissue is collagen. Copper is an essential cofactor for expression of enzyme lysyl oxidase. Lysyl oxidase makes collagen resistant to degradation by collagenase. Cu may be involved in this process for cross linking of collagen. This mechanism was explained by Khanna et al (2006) [33] who demonstrated that copper upregulated the expression of the enzyme lysyl oxidase in the oral mucosa leading to fibrosis. The probable explanation is that copper stabilizes the enzyme activity by increasing its half-life. The other explanation is that at the molecular level, the N-terminus ofexon-1 of lysyl oxidase molecule has copper binding site and this interaction may upregulate the expression of enzymes at cellular level[34]. As understood, abnormal collagen deposition is a hallmark of OSMF.As per Mathew et al

(2014)[35], copper levels in raw areca nuts and commercial areca nut products (like gutka) are significantly higher. Copper is also an important component of betel nut. High levels of copper in areca nut plays an initiating role in stimulation of fibrogenesis by upregulation of lysyl oxidase and thereby causing inhibition of degradation of collagen. Also it is understood that for remodeling and phagocytosis of collagen, fibroblasts are required. In OSMF, these fibroblasts are affected and phenotypically changed and therefore they cannot degrade collagen thereby making it highly resistant to remodeling and phagocytosis [26].

It was observed that patients when subjected to a diet with slightly elevated Cu levels compared to average diets, such as consuming Cu water, the concentration of Cu in local tissues rises, there by elevating the risk of OSMF development in the oral mucosa.

Moreover, it has been proposed that the onset of OSMF syndrome hinders Cu excretion.

The rise in serum copper may also be due to increased production of copper containing ceruloplasmin by liver as an inflammatory response or due to decrease in the catabolism of the serum ceruloplasmin [36].Our findings of elevated copper levels in OSMF coincides with the findings of Varghese et al (1987)[37], who reported elevated levels of copper in in oral submucous fibrosis and with Trivedy et al (2000)[38]who performed mass absorption spectrometry (MAS) in biopsy samples to estimate the concentrations of copper in OSMF patients and reported similar increase in patients with OSMF as a result of chewing areca nut chewing. This is due to the fact that copper is an initiating factor in OSF and plays a role in stimulating fibrogenesis by the upregulation of lysyl oxidase activity.

Hosthor et al (2014)[24] and Jani et al(2017)[39] also reported that mean serum copper level increases while the mean serum iron level decreases with the advancement in the severity of clinical and histological stages of OSMF. Our findings are in agreement with many other researchers Luquman et al (2004) [40] who reported that the serum copper level in OSMF showed increase values when compare to normal controls. This could cause an upregulation of enzyme lysyl oxidase leading to cross linking of collagen and elastin. However, their findings about the serum iron levels were different such that it did not show a statistically significant reduction when compared to normal control, except in case of clinical anemia. Similar to our study, Tadakamadla et al (2011)[6] employed atomic absorbtion spectrophotometry to estimate and compare the levels of serum copper and iron among subjects with OSMF of different clinical stages and healthy controls.

Therefore, it is well understood that serum copper, and iron levels could be used as a potential prognostic and diagnostic markers in OSMF patients. Atomic Absorption method was also employed by Neethi et al (2013) whose findings were coincidental with our findings and suggested that derangements noted in the serum copper levels could be correlated with diseased progression and possibly explain the transformation of OSMF into malignancy. Thus, they can be used as prognostic markers and can be of value for proactive intervention. In contrast to our findings, Ravikant et al (2021) reported a lower serum levels of both copper and iron. But they could not provide a definite explanation for the same.

**Conclusion**

OSMF is a complex precancerous condition that impacts the oral cavity and oropharynx. Increased number of studies is being done one estimating trace elements in relation to OSMF to gain a better understanding of their essential functions and to assess their importance in the

development, severity, and treatment of this potentially premalignant oral condition. Trace elements particularly Cu and iron play a vital role in collagen production, immune response, tissue repair, and antioxidant defense. Their significance arises from the potential for them to serve as diagnostic and prognostic markers, guide treatment strategies, and offer insights into preventive measures. By gaining a comprehensive understanding of how trace elements affect this condition, researchers aim to enhance methods for diagnosing, treating, and preventing

OSMF. This study has addressed the trace elements in great detail. Increased levels of copper with subsequent increase in copper levels with severity of OSMF along with decreased levels of iron and further decrease with increasing severity of OSMF as compared to healthy individuals, indicate that there is a considerable risk of the condition advancing to cancer also nutritional deficiencies can worsen the condition and hinder the body's ability to repair and regenerate the oral tissues affected by OSMF. To improve the prognosis, aggressive measures should be implemented for early diagnosis. To manage and prevent OSMF, it is crucial to have a balanced diet that includes these trace elements, receive appropriate medical care, and avoid risk factors such as areca nut and tobacco use. However, further studies with larger sample size is required for better findings and interpretation.

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