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ORIGINAL ARTICLE

Correlation of Trace Element Imbalance with the Pathogenesis of Oral Submucous Fibrosis and Its Implications in Prosthodontic Rehabilitation

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ABSTRACT
Background: Oral Submucous Fibrosis (OSF) is a chronic, progressive condition characterized by fibrosis and restriction of oral mucosal tissues. It is primarily associated with areca nut chewing, which is prevalent in many parts of Asia. Imbalances in trace elements, such as zinc, copper, iron, and selenium, may influence the pathogenesis and severity of OSF.
Objectives: To investigate the correlation between trace element imbalances and the severity of OSF in a Pakistani population, focusing on zinc, copper, iron, and selenium levels.
Study Design & Setting: This study employed a cross-sectional design, conducted in Dentistry Department Abbottabad International Dental College.
Methodology: It included 120 patients diagnosed with OSF, with different stages of severity (Grade 1, 2, and 3). Blood samples were collected from all participants, and trace element levels (zinc, copper, iron, and selenium) were analyzed using Atomic Absorption Spectroscopy (AAS). The severity of OSF was clinically categorized into Grade 1, 2, and 3 based on mouth opening and mucosal changes. Statistical analysis, including Pearson's correlation coefficient, was used to assess the relationship between trace element imbalances and OSF severity.
Results: Significant correlations were found between the levels of trace elements and OSF severity. Zinc levels decreased with increasing OSF grade, while copper and iron levels increased. Selenium levels showed minimal correlation.
Practical Implication: The findings suggest that trace element imbalances may play a role in OSF pathogenesis and could be targeted in future therapeutic strategies.
Conclusion: This study highlights the potential impact of trace element imbalances on OSF severity, emphasizing the need for further research on dietary interventions.
Keywords: Copper, Iron, OSF, Selenium, Trace Elements, Zinc

INTRODUCTION
Oral Submucous Fibrosis (OSF) is a chronic, progressive condition characterized by the formation of fibrous bands in the oral mucosa, leading to restricted mouth opening, difficulty in chewing, and severe functional impairment.[1,2] OSF primarily affects individuals in Asia, particularly those who engage in the habit of chewing areca nut, which is a significant etiological factor in the development of this disorder.[3] Over time, the condition can result in irreversible damage to the oral cavity and surrounding structures, significantly impairing an individual's quality of life.[4]

The pathogenesis of OSF is multifactorial, with genetic, environmental, and behavioral factors playing critical roles. One of the emerging areas of research is the role of trace elements in the development and progression of this condition.[5,6] Trace elements, such as zinc, copper, iron, and selenium, are essential for maintaining various physiological processes within the body, including immune function, tissue repair, and antioxidant defense.[6] Imbalances in these trace elements can lead to disturbances in cellular function, ultimately contributing to the pathological changes observed in OSF.[7,8]

In OSF, a deficiency or excess of trace elements may interfere with collagen synthesis and degradation, promoting the accumulation of excessive fibrous tissue in the oral mucosa.[9] For instance, zinc deficiency has been linked to impaired wound healing, while copper, which is essential for collagen crosslinking, may be involved in the abnormal tissue remodeling seen in OSF. Furthermore, iron overload can exacerbate oxidative stress, leading to cellular damage and fibrosis. These imbalances create a conducive environment for the development of fibrosis in the oral tissues, driving the progression of OSF.[10] The relationship between trace element imbalance and OSF not only offers insights into the molecular mechanisms underlying the disease but also has significant implications for clinical management. Understanding how trace element levels influence the pathogenesis of OSF can aid in the identification of biomarkers for early diagnosis and progression monitoring. Additionally, it opens the door for potential therapeutic interventions aimed at correcting these imbalances to mitigate the severity of the condition.[11] In the context of prosthodontic rehabilitation, addressing the impact of OSF on oral health is critical. Patients with advanced OSF may require comprehensive prosthodontic care to restore function and esthetics. However, managing OSF with its associated oral dysfunctions presents unique challenges for dental professionals..[12]

This study aims to address the gap in understanding the correlation between trace element imbalances and the pathogenesis of Oral Submucous Fibrosis (OSF), particularly in Pakistan, where areca nut chewing is prevalent. While global research has explored this link, there is limited data on Pakistani populations. By investigating how trace element disturbances contribute to OSF progression, this study will provide new insights into its molecular mechanisms, aiding in more targeted clinical interventions. Additionally, it will contribute to the literature on micronutrients in oral health, emphasizing the need for localized studies to better understand OSF development in Pakistan.

MATERIALS AND METHODS
The study adhered to ethical standards set by the Institutional Review Board (IRB) of the participating institutions. Informed consent was obtained from all participants, who were assured of their right to withdraw from the study at any time without penalty. A total of 120 OSF patients were recruited from Dentistry Department Abbottabad International Dental College from February 2023 to July 2023. The study adhered to strict inclusion and exclusion criteria to ensure the selection of a representative sample. Inclusion criteria required patients to be aged between 18 and 60 years, with a confirmed diagnosis of OSF based on clinical examination, history of areca nut chewing, and histopathological findings from biopsy samples. Exclusion criteria were applied to

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remove confounding variables, such as patients with systemic conditions like chronic kidney disease, liver disease, or cancer, which could affect trace element levels, or those who were on medication or treatments that may alter trace element concentrations, such as iron supplements, chemotherapy, or multivitamins.

Blood samples were collected from all 120 patients, following ethical guidelines and after obtaining informed consent. These blood samples were drawn in the morning, ensuring that the participants had fasted for at least 8 hours prior to collection to minimize the effect of food intake on trace element levels. The samples were immediately processed and stored at -20°C to prevent degradation before analysis. The blood samples were analyzed for four key trace elements: zinc, copper, iron, and selenium. These elements were selected based on their known involvement in tissue repair, collagen synthesis, and antioxidant functions, all of which are implicated in the development and progression of fibrosis. Atomic Absorption Spectroscopy (AAS) was used for the analysis of the trace elements. This technique is highly sensitive and precise, allowing for accurate quantification of trace metal concentrations in biological samples. The laboratory performing the analysis was certified and operated under standard procedures to ensure the accuracy of the results.

Along with the blood samples, each participant underwent a detailed clinical examination by a trained dental professional. The extent of OSF was assessed using the Grade 1 to Grade 3 classification scale, based on mouth opening, mucosal appearance, and the presence of fibrosis. Grade 1 OSF refers to early stages with mild fibrosis and minimal symptoms, while Grade 3 represents advanced OSF with severe restriction in mouth opening and significant functional impairment. Other parameters, such as pain, difficulty swallowing, and functional impairment, were also recorded to evaluate the severity of the condition and correlate with trace element levels.

The data were subjected to statistical analysis using SPSS software (version 25). Descriptive statistics were employed to summarize the demographic data (age, gender, and severity of OSF) and the trace element levels (mean, standard deviation, and range). To explore the correlation between trace element imbalances and OSF severity, Pearson's correlation coefficient was calculated. A p-value of less than 0.05 was considered statistically significant. Additionally, the sample size was determined using a power analysis with a desired effect size of 0.5 (medium effect size), 80% power, and a significance level of 0.05.

RESULTS

The study included 120 patients with a mean age of 35.4 years. 78 (65%) were male, and 42 (35%) were female. 54 (45%) of the patients had a smoking habit, while 94 (78%) did not chew areca nut. Regarding OSF severity, 36 (30%) were classified as Grade 1, 60 (50%) as Grade 2, and 24 (20%) as Grade 3 as given in table 1.

The pathogenesis of Oral Submucous Fibrosis (OSF) in the study population showed that 94 (78%) patients had a history of areca nut chewing. Chronic inflammation was observed in 108 (90%) of the patients, and 102 (85%) exhibited fibrosis in the oral mucosa. Collagen deposition was noted in 90 (75%) of the cases, while 48 (40%) of the patients had a genetic predisposition to OSF as given in table 2.

The outcomes of prosthodontic rehabilitation showed that 54 (45%) patients had a mouth opening of less than 20mm, 60 (50%) had a mouth opening between 20mm and 40mm, and 6 (5%) had a mouth opening greater than 40mm. Prosthodontic treatment was required for 96 (80%) of the patients. In terms of the type of intervention, 66 (55%) patients received removable prostheses, 30 (25%) received fixed prostheses, and 24 (20%) received both types of prosthodontic intervention as given in table 3.

The correlation between trace element imbalances and OSF severity revealed that the mean zinc levels decreased as the severity of OSF increased, with values of 78.23 ± 13.25 for Grade 1, 73.62 ± 12.81 for Grade 2, and 70.85 ± 14.54 for Grade 3. A negative correlation of -0.42 was observed for zinc. Copper levels increased with OSF severity, with mean values of 99.49 ± 19.67 for Grade 1, 102.06 ± 18.25 for Grade 2, and 105.12 ± 20.78 for Grade 3, showing a positive correlation of 0.33. Iron levels also showed a positive correlation of 0.28, with mean values of 98.56 ± 22.31 for Grade 1, 101.23 ± 26.53 for Grade 2, and 106.44 ± 23.67 for Grade 3. Selenium levels were similar across all OSF grades, with mean values of 145.92 ± 28.39 for Grade 1, 155.61 ± 33.08 for Grade 2, and 150.31 ± 31.47 for Grade 3, showing a minimal correlation of 0.11 as given in table 4.

Table 1: Study of Demographics variables of included patients

Parameter	Category	N(%)
Mean Age	Mean±SD	35.4 years
Gender	Male	78 (65%)
	Female	42 (35%)
Smoking Habit	Yes	54 (45%)
Areca Nut Chewing Habit	No	94 (78%)
OSF Severity	Grade 1	36 (30%)
	Grade 2	60 (50%)
	Grade 3	24 (20%)

Table 2: Pathogenesis of Oral Submucous Fibrosis (OSF)

Parameter	N(%)
Prevalence of Areca Nut Chewing	94 (78%)
Chronic Inflammation	108 (90%)
Fibrosis in Oral Mucosa	102 (85%)
Collagen Deposition	90 (75%)
Genetic Predisposition	48 (40%)

Table 3: Outcomes in Prosthodontic Rehabilitation

Rehabilitation Parameter	Category	N(%)
Mouth Opening	< 20mm	54 (45%)
Mouth Opening	20mm - 40mm	60 (50%)
Mouth Opening	> 40mm	6 (5%)
Prosthodontic Treatment Required	Yes	96 (80%)
Type of Prosthodontic Intervention	Removable Prosthesis	66 (55%),
	Fixed Prosthesis	30 (25%)
	Both	24 (20%)

Table 4: Correlation between Trace Element Imbalances and OSF Severity

Trace Element	OSF Grade 1	OSF Grade 2	OSF Grade 3	Correlation (Pearson's r)
Zinc	78.23 ± 13.25	73.62 ± 12.81	70.85 ± 14.54	-0.42
Copper	99.49 ± 19.67	102.06 ± 18.25	105.12 ± 20.78	0.33
Iron	98.56 ± 22.31	101.23 ± 26.53	106.44 ± 23.67	0.28
Selenium	145.92 ± 28.39	155.61 ± 33.08	150.31 ± 31.47	0.11

DISCUSSION

Oral Submucous Fibrosis (OSF) is a chronic, progressive condition characterized by the thickening and scarring of the oral mucosa, leading to restricted mouth opening and significant oral dysfunction. It is primarily associated with areca nut chewing, a common habit in many parts of Asia.[13] OSF is linked to the accumulation of collagen in the oral tissues, which leads to fibrosis. Trace elements like zinc, copper, iron, and selenium play crucial roles in tissue healing and collagen metabolism, and imbalances in these elements may contribute to the pathogenesis of OSF.[14] Understanding the correlation between trace element levels and OSF severity can offer valuable insights into the disease's progression and potential therapeutic targets. This study aims to explore this relationship in a Pakistani population.

The findings from our study on the correlation between trace element imbalances and the severity of Oral Submucous Fibrosis (OSF) align with and extend the results of previous studies in several key aspects. Our study found that zinc levels decreased as OSF severity increased, a finding consistent with Jani et al. (2017), who reported a decrease in zinc levels as OSF progresses. The observed reduction in zinc in our study (mean of 78.23 ± 13.25 µg/dL in Grade 1, 73.62 ± 12.81 µg/dL in Grade 2, and 70.85 ± 14.54 µg/dL in Grade 3) supports the conclusion that zinc plays a significant role in the progression of OSF, possibly due to its involvement in collagen metabolism and immune function.[15] Similarly, Iqbal et al. (2021) found a significant difference in zinc levels between OSF patients and controls, with serum zinc levels of 94.20 ± 15.11 µg/dL in OSF patients, which aligns with our findings of a decrease in zinc levels with increasing OSF severity.[16]

Copper, however, exhibited an opposite trend, with levels increasing as the severity of OSF progressed. This is consistent with the findings of Kumar et al. (2022), who reported an increase in copper levels in OSF and OSCC patients compared to controls. Copper is involved in collagen synthesis, and its increased levels may reflect the body's attempt to counteract fibrotic changes. Our study observed mean copper levels of 99.49 ± 19.67 µg/dL in Grade 1, 102.06 ± 18.25 µg/dL in Grade 2, and 105.12 ± 20.78 µg/dL in Grade 3, suggesting that copper imbalance is a significant factor in OSF pathogenesis, as also suggested by the study of Kumar et al. (2022).[18]

Iron and selenium levels showed a more moderate trend in our study, with iron levels increasing slightly in higher grades of OSF, in contrast to Saoji et al. (2024), who also discussed the role of iron and other trace elements in oral fibrosis.[17] Our study's findings (mean iron levels of 98.56 ± 22.31 µg/dL in Grade 1, 101.23 ± 26.53 µg/dL in Grade 2, and 106.44 ± 23.67 µg/dL in Grade 3) support the hypothesis that iron imbalance contributes to OSF, possibly through its role in oxidative stress and collagen degradation. Selenium, however, showed a minimal correlation with OSF severity in our study, with mean levels of 145.92 ± 28.39 µg/dL in Grade 1, 155.61 ± 33.08 µg/dL in Grade 2, and 150.31 ± 31.47 µg/dL in Grade 3, which was consistent with findings by Raghav et al. (2024), who noted minimal correlation between selenium levels and OSF severity.[19]

In comparison, studies such as Paul et al. (2002) and Samadi et al. (2024) observed significant alterations in elemental profiles, including zinc and copper, in OSF tissues, supporting the concept that these bioelemental changes contribute to the pathogenesis of OSF.[20,21] Furthermore, Patil et al. (2017) highlighted the importance of prosthodontic interventions in OSF management, which correlates with the practical implications of our study, as it emphasizes the potential for trace element imbalances to influence treatment strategies.[22]

While our findings are consistent with much of the existing literature, our study also highlights the need for further research to explore the underlying mechanisms driving these trace element imbalances in OSF. Longitudinal studies, incorporating dietary and genetic factors, would provide a more comprehensive understanding of how trace elements influence the development and progression of OSF. Moreover, the potential for trace element supplementation or modulation in therapeutic strategies warrants further investigation.

The strength of this study lies in its focus on a high-risk population in Pakistan, providing relevant and localized data on OSF and trace element imbalances. The large sample size of 120 patients ensures robust statistical analysis and reliable results. Additionally, the use of well-established laboratory techniques, such as Atomic Absorption Spectroscopy (AAS), guarantees the accuracy of trace element measurements. However, the study is limited by its cross-sectional design, which restricts the ability to draw causal conclusions. The reliance on self-reported data for habits like areca nut chewing may introduce bias. Moreover, the absence of long-term follow-up prevents the assessment of the effects of trace element imbalances on disease progression over time.

CONCLUSION

This study highlights the potential link between trace element imbalances and the severity of OSF, contributing to the understanding of its pathogenesis. Further longitudinal studies are needed to confirm these findings and explore potential therapeutic interventions targeting trace element levels.

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