RESEARCH ARTICLE

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Serum Homocysteine and Its Diagnostic Significance in Oral Submucous Fibrosis: A Cross-Sectional Study

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Abstract

Background: Oral Submucous Fibrosis (OSMF) is a chronic, progressive, potentially malignant disorder of the oral cavity, predominantly associated with areca nut chewing. Oxidative stress and nutritional deficiencies, particularly of folate and vitamin B12, have been implicated in its pathogenesis. Homocysteine (Hcy), a sulfur-containing amino acid, serves as a sensitive biomarker for folate and B12 metabolism and is known to contribute to oxidative stress when elevated. This study aimed to evaluate the serum homocysteine levels in OSMF patients and assess its potential as a biochemical marker for disease severity and progression. **Materials and methods:** A comparative study was conducted on 60 participants, including 30 clinically and histopathologically confirmed OSMF patients and 30 healthy age- and gender-matched controls. Serum homocysteine levels were estimated using ELISA. Clinical grading of OSMF was based on interincisal distance. Statistical analysis was performed using t-tests, ANOVA, and Receiver Operating Characteristic (ROC) curve analysis to determine the diagnostic utility of homocysteine levels. **Results:** Mean serum homocysteine levels were significantly higher in the OSMF group (24.17 µmol/L) compared to controls (10.80 µmol/L) ($p < 0.001$). ANOVA revealed a progressive increase in homocysteine levels across OSMF grades: Grade I – 19.05 µmol/L, Grade II – 23.65 µmol/L, Grade III – 28.92 µmol/L, and Grade IV – 36.98 µmol/L. ROC analysis showed an AUC of 1.00, with an optimal cut-off of 15.90 µmol/L yielding 100% sensitivity and specificity for distinguishing OSMF from controls. **Conclusion:** Elevated serum homocysteine levels are significantly associated with OSMF and correlate with disease severity. Homocysteine may serve as a promising, non-invasive biochemical marker for early detection and progression monitoring in OSMF patients.

Keywords: Biomarkers- Homocysteine- Oral Submucous Fibrosis- Oxidative Stress

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Introduction

Oral submucous fibrosis (OSMF) is a chronic, progressive, and potentially malignant disorder of the oral mucosa, first described by Schwartz in 1952 as a collagen metabolic disorder [1]. Historical references date back to 600 BC, where Sushruta described a similar condition called "Vidari" [2]. The term "oral submucous fibrosis" was later coined by Joshi [3], and Pindborg and Sirsat defined it "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 a juxtaepithelial 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" [4].

Oral submucous fibrosis (OSMF) is a well-recognized potentially malignant disorder, with its malignant potential first described by Paymaster [5]. The malignant transformation rate (MTR) of OSMF has been evaluated in numerous studies across diverse populations. A long-term follow-up study reported an MTR of 7.6% over a 17-year period, while another study from India observed a lower transformation rate of 2.6% [6]. Among Indian populations, the highest MTR of 7.6% was reported by the International Agency for Research on Cancer (IARC) [7]. It is estimated that between 0.2% and 1.2% of the Indian population is affected by OSMF. An epidemiological survey conducted a decade ago revealed over 250,000 reported cases nationwide, with a prevalence of up to 4% in certain regions of Kerala. More recently, a marked increase in OSMF prevalence has been observed in other Indian states such as Gujarat, Bihar, Maharashtra, and

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Madhya Pradesh [8]. Given its malignant potential, timely recognition and risk assessment of OSMF are crucial for early intervention, which can significantly improve treatment outcomes and enhance patients' quality of life.

The pathogenesis of OSMF is multifactorial, involving chronic inflammation, juxtaepithelial fibrosis, altered collagen metabolism, nutritional deficiencies, and epigenetic changes [9]. Reactive oxygen species (ROS) and oxidative stress have been implicated as key contributors to disease progression by inducing lipid peroxidation, fibroblast activation, and extracellular matrix accumulation [10, 11]. Given this complex biochemical milieu, recent studies have focused on identifying metabolic and oxidative stress markers that could support early detection and clinical risk stratification in OSMF.

Recent advances in molecular biology have emphasized the role of metabolic and inflammatory markers in the progression of potentially malignant disorders. The methionine cycle, one of the key metabolic pathways implicated in carcinogenesis, yields homocysteine (Hcy) as an intermediate product [12]. Homocysteine is a sulfur-containing amino acid influenced by multiple lifestyle and nutritional factors, including vitamin B12 and folate status [13]. Elevated serum homocysteine has been extensively studied as a biomarker for systemic diseases such as cardiovascular disorders and neurodegeneration, and more recently, has gained interest for its role in oncogenesis due to its involvement in DNA methylation, oxidative stress, and endothelial dysfunction [14]. While studies have explored the role of homocysteine in systemic diseases and malignancies, its association with oral potentially malignant disorders (PMDs), including OSMF, remains under-investigated. Preliminary evidence suggests that elevated homocysteine levels may reflect impaired methylation and increased oxidative stress, both of which are relevant to the pathogenesis of OSMF. However, very few studies have quantitatively evaluated serum homocysteine levels in OSMF patients or examined its potential utility as a diagnostic or prognostic biomarker. Hence, the objective of the present study was to evaluate the association between serum homocysteine levels and oral submucous fibrosis (OSMF), and to explore its potential role as a biochemical marker in the pathogenesis and progression of this potentially malignant disorder. This could contribute to early detection strategies and better clinical risk assessment of OSMF.

Materials and Methods

This comparative study was conducted on patients with oral submucous fibrosis (OSMF) who attended the Kamineni Institute of Dental Sciences, Narketpally, Nalgonda, following approval from the Institutional Ethical Committee (IEC No. KIDS/IEC/2015/16). A total of 60 subjects were enrolled and divided into two groups: Group A comprised 30 patients diagnosed with OSMF according to the classification by Khanna and Andrade [15], while Group B included 30 age- and gender-matched healthy controls. Based on prior literature, an expected large effect size (Cohen's $d \approx 0.8$) was assumed. Power analysis using a two-tailed t-test with $\alpha = 0.05$ and power $(1-\beta) = 0.80$ indicated a minimum sample size of 26 per group. To account for variability and potential dropouts, 30 participants were recruited per group, ensuring adequate power to detect significant differences. Group A subjects were further clinically graded (I to IV) based on interincisal mouth opening as follows:

Clinical grading based on interincisal distance

GRADE I - Interincisal distance >35mm
GRADE II - Interincisal distance 26-35mm
GRADE III - Interincisal distance 15-25mm
GRADE IV - Interincisal distance < 15mm

Exclusion criteria

Patients with systemic disorders such as cardiovascular disorders, diabetes, hypertension, collagen disorders, and any other pre-cancerous lesions and conditions and other autoimmune disorders, osteoporosis, or other malignancies were excluded.

Serum collection

Following informed consent, venous blood samples were collected from participants under strict aseptic conditions using spirit-soaked cotton. A 24-gauge needle was used to withdraw 4 mL of blood from each subject. The collected samples were centrifuged at 2500 rpm for 15 minutes to separate the serum. The resulting supernatant was carefully extracted and stored at –80 °C until further analysis. Serum homocysteine levels were estimated using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

Homocysteine estimation

The serum samples were brought to room temperature prior to analysis. A total of 100 µL of each test specimen was added to the wells of an antibody-coated 96-well microtiter plate and incubated for 1 hour at approximately 25°C. After incubation, the wells were washed thoroughly to remove unbound material. Subsequently, 100 µL of detection antibody was added to each well and incubated for an additional hour at ~25°C, followed by a second washing step. Then, 100 µL of streptavidin–HRP conjugate was added to each well and incubated for 30 minutes at ~25°C. After another wash, 100 µL of TMB (3,3′,5,5′-Tetramethylbenzidine) substrate solution was added to each well and the plate was incubated in the dark for 15 minutes at ~25°C. To terminate the enzymatic reaction, 50 µL of stop solution was added to each well, resulting in the development of a yellow-colored product. The intensity of the color, proportional to the concentration of homocysteine, was measured using an ELISA microplate reader at absorbance wavelength of 450 nm.

The optical density (OD) values obtained from the serum samples were plotted against the standard curve to determine the concentration of homocysteine, expressed in µmol/L. The resulting data were analyzed using IBM SPSS Statistics for Windows, Version 19.0 (Released 2010; IBM Corp., Armonk, NY, USA). Descriptive statistical analysis was performed to calculate the mean, median, interquartile range (IQR), and standard deviation

(SD). Group comparisons were assessed using one-way analysis of variance (ANOVA) followed by post hoc testing to determine statistical significance. To evaluate the diagnostic accuracy of serum homocysteine levels, receiver operating characteristic (ROC) curve analysis was conducted. The optimal cutoff point was identified based on the maximum positive likelihood ratio (PLR), calculated as the ratio of sensitivity to (1 – specificity), providing insight into the biomarker's discriminative power.

Results

The present study included a total of 60 participants, among which a total of 30 individuals with clinically and histopathologically confirmed oral submucous fibrosis (OSMF) and 30 healthy controls were included in the study. Among 30 patients from group A, 9 patients were under Grade-I, 13 patients were under Grade-II, 6 patients were under Grade-III, 2 patients were under Grade-IV. Demographic data of the individuals is given in Table 1.

Table 1. Demographic Data of the Individuals

Data	OSMF	Controls
Number	30 cases	30 cases
Age (mean)	33.01 years	31.05 years
Males	29	26
Females	1	4
Grading		
Grade I	9	-
Grade II	13	-
Grade III	6	-
Grade IV	2	-

The t- test analysis performed for homocysteine levels in OSMF and control groups showed that the mean values of OSMF group (24.172 µmol/Litre) are highly significant compared to that of control group (10.797 µmol/Litre) (Table 2).

Comparison of homocysteine values in different grades of OSMF using ANOVA showed a highly statistical significant difference with the mean serum homocysteine levels for Grade I at 19.0466 µmol/liter, Grade II at 23.6461 µmol/liter, 28.921 µmol/liter for Grade III, and 36.98 µmol/liter for grade IV. Table 3 indicate that the mean serum homocysteine levels for all the grades.

To assess the diagnostic performance of serum homocysteine in distinguishing OSMF cases from controls, a Receiver Operating Characteristic (ROC) curve analysis was conducted. The Area Under the Curve (AUC) was 1.00, indicating perfect diagnostic accuracy (Figure 1). The optimal cutoff value was identified as 15.90 µmol/L, representing the threshold with the maximum true positive rate and minimum false positive rate. At this cutoff, both sensitivity and specificity were 100%, clearly differentiating OSMF cases from controls. The 95% confidence interval for the AUC was [1.00, 1.00], demonstrating statistical robustness and complete group separation.

Table 2. t-test Analysis of Homocysteine Levels in Oral Submucous Fbrosis Patients and Healthy Controls

Group	Sample size (n)	Mean	Standard Deviation	t value	p value
OSMF	30	24.172667	5.413513	12.9924	< 0.00001
Controls	30	10.797333	1.577447		

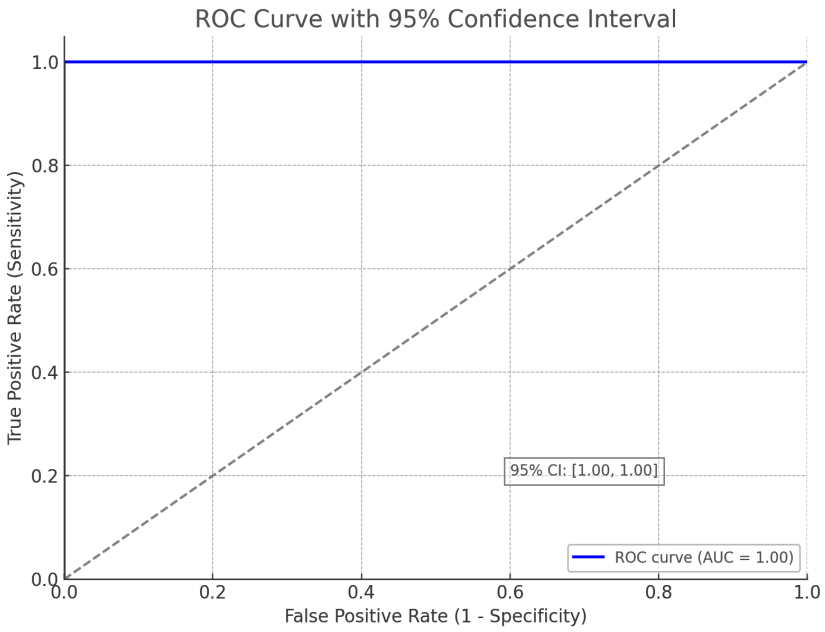

Figure 1. Sensitivity and Specificity of Homocysteine assessed by ROC Curve Analysis

Table 3. Comparison of Homocysteine Levels in Different Grades of OSMF by One- Way ANOVA Test. *p value is significant (p<0.01)

Groups	Number	Sum	Mean		
Grade I	9	171.42	19.04667		
Grade II	13	307.7	23.66923		
Grade III	6	173.53	28.92167		
Grade IV	2	73.96	36.98		
Source of Variation	SS	df	MS	F	p value
Between Groups	703.0831	3	234.361	38.92748	9.23E-10*
Within Groups	156.5318	26	6.020453		
Total	859.6149	29			

Discussion

Oral Submucous Fibrosis (OSMF) is a well-recognized potentially malignant disorder that may progress to Oral Squamous Cell Carcinoma (OSCC), influenced by various factors such as betel quid chewing, tobacco use, nutritional deficiencies, and microbial infections [16]. Among these, nutritional deficiencies particularly of essential vitamins and minerals play a crucial role in inducing pathological changes within the oral cavity. Deficiencies in key nutrients can exacerbate OSMF symptoms, promote oxidative DNA damage, and increase the risk of malignant transformation. One key mechanism linking nutritional deficiency to carcinogenesis is impaired DNA methylation, often resulting from inadequate folate levels [17]. Serum homocysteine is a sensitive and reliable biomarker of folate status. Folate deficiency is frequently associated with elevated homocysteine levels (hyperhomocysteinemia), and increased folate intake has been shown to reduce these levels. Inadequate folate can also lead to uracil misincorporation into DNA, contributing to genomic instability. Elevated homocysteine has been associated with a range of malignancies, including colorectal and cervical cancers, and disruptions in the methionine cycle are believed to contribute to the development of breast and pancreatic cancers. Although moderate folate deficiency may not be independently mutagenic, it can interact synergistically with environmental or genetic risk factors to accelerate tumor progression. Based on this understanding, the present study was undertaken to evaluate serum homocysteine levels as a potential biochemical marker in patients with OSMF [14].

The present study included a total of 60 participants, comprising 30 individuals with clinically and histopathologically confirmed oral submucous fibrosis (OSMF) and 30 healthy controls. Among the OSMF group (Group A), patients were categorized based on clinical grading: 9 were classified under Grade I, 13 under Grade II, 6 under Grade III, and 2 under Grade IV. Independent t-test analysis revealed that the mean serum homocysteine levels were significantly elevated in the OSMF group (24.172 µmol/L) compared to the control group (10.797 µmol/L). Further, one-way ANOVA demonstrated a statistically significant difference in homocysteine levels across the clinical grades of OSMF. The mean serum homocysteine concentrations were 19.05 µmol/L for Grade I, 23.65 µmol/L for Grade II, 28.92 µmol/L for Grade III, and 36.98 µmol/L for Grade IV.

Similar to the present study, Narang et al. [18] evaluated 50 clinically and histopathologically diagnosed cases of oral submucous fibrosis who were not undergoing treatment. Their findings demonstrated elevated homocysteine levels, although no statistically significant correlation was observed with clinical or histological staging. They concluded that hyperhomocysteinemia in OSMF, likely resulting from chronic inflammation, could serve as a prognostic marker for therapeutic response and disease severity [18].

In a cross-sectional study conducted by Bais et al. [14] serum homocysteine levels in 50 untreated OSMF patients were assessed. The mean homocysteine level was 24.1 µmol/L, with higher levels observed in patients of stage IV (31.02±6.33) than stage III (26.98±8.67) and II (25.47±7.72). However, no statistically significant differences were found across stages or between genders. The study highlights the need for larger, longitudinal studies to confirm homocysteine's role as a biomarker in OSMF [14].

Vanjani et al. conducted a study involving 60 participants to evaluate serum homocysteine and Vitamin B12 levels using a chemiluminescence immunoassay. The results showed significantly elevated homocysteine levels in patients with oral submucous fibrosis (OSMF) compared to healthy controls (P = 0.014). A significant inverse correlation was observed between homocysteine and Vitamin B12 levels (P = 0.01), whereas no significant association was found between homocysteine levels and the clinical severity of OSMF (P = 0.806). The study suggests that serum homocysteine may serve as a potential biomarker for OSMF; however, Vitamin B12 deficiency and other systemic conditions must be excluded before considering its clinical application [13].

Zhang et al. [19] investigated the association between plasma levels of folate, vitamin B6, vitamin B12, and homocysteine, and the risk of breast cancer. Their findings revealed that elevated plasma concentrations of folate and vitamin B12 were associated with a reduced risk of developing breast cancer. However, no significant association was observed between homocysteine levels and cancer risk. This contradicts more recent suggestions proposing homocysteine as a potential tumor marker, highlighting the complexity and context-specific nature

of its role in different pathological conditions [19].

In the study by Almadori et al. [20], 144 Head and Neck Squamous Cell Carcinoma (HNSCC) patients and 40 with laryngeal leukoplakia were compared with smoker and nonsmoker controls. Serum folate levels were significantly lower in both patient groups compared to controls. Homocysteine levels were significantly elevated only in HNSCC patients. Vitamin B12 levels showed no significant difference across all groups. The study suggests folate deficiency as a potential risk factor and highlights homocysteine as a possible marker influenced by tumor phenotype. While both the studies report elevated homocysteine in cancerous conditions, our study on OSMF patients also found raised homocysteine levels but no correlation with disease severity. Unlike the HNSCC study, we observed a significant inverse relationship between homocysteine and Vitamin B12 levels, suggesting a possible nutritional or metabolic influence in OSMF pathogenesis [20].

A study by Eleftheriadou et al. [12] evaluated serum folate and homocysteine levels in 150 untreated HNSCC patients compared to 150 healthy controls (smokers and non-smokers). HNSCC patients had significantly lower folate and higher homocysteine levels than both control groups ($p<0.001$). Smoking alone was also associated with decreased folate and increased homocysteine levels. A significant correlation was found between the presence of HNSCC and altered serum levels. Similar to our findings in OSMF patients, this study also reported elevated homocysteine levels, reinforcing its potential role in oral precancer and cancer. This study showed a positive correlation between HNSCC and homocysteine levels, possibly due to the malignant nature of the disease. Both studies support the idea that homocysteine may be a useful biomarker, though influenced by smoking and folate status [12].

Ferroni et al. [21] assessed homocysteine levels in 47 cancer patients in relation to MTHFR polymorphisms, folate, and inflammatory markers. Hcy levels were significantly higher in cancer patients ($p = 0.04$) and correlated with IL-6, TNF-alpha, and folate levels. Through Multivariate analysis it was determined that TNF-α ($p=0.014$) and folate ($p=0.019$) were significant indicators of elevated Hcy levels in cancer patients [21].

Erugula et al. [22] in their study evaluated serum homocysteine and folate levels among 30 OSCC patients, 15 smokers without OSCC, and 15 healthy non-smokers. Results showed significantly elevated Homocysteine and reduced folate levels in OSCC patients compared to both control groups ($p<0.001$). The findings suggest that alterations in Hcy and folate levels may serve as potential biochemical tumor markers for OSCC, offering insight into disease onset and progression [22].

The cut-off value of homocysteine levels in the present study was determined to be 15.90 µmol/L, aligning closely with the established threshold for hyperhomocysteinemia (HHcy), which is defined as blood plasma levels exceeding 15 µmol/L. According to existing literature, HHcy is a systemic condition associated with a range of severe pathologies, including neurodegenerative diseases, cardiovascular disease, thrombosis, osteoporosis, and various cancers [23]. Several risk factors such as aging, smoking, and notably, oxidative stress are known to exacerbate HHcy. This cut-off value reinforces our findings, suggesting that elevated homocysteine levels may play a significant role in the pathogenesis and progression of OSMF. Homocysteine, a sulfur-containing amino acid, contributes to oxidative stress by promoting the formation of reactive oxygen species (ROS) and impairing antioxidant defences [24]. In OSMF, a chronic, progressive, and precancerous condition characterized by mucosal inflammation and fibrosis oxidative stress is a central pathogenic mechanism. Elevated homocysteine may amplify this oxidative burden, fostering tissue fibrosis, epithelial atrophy, and potentially aiding malignant transformation. These findings support the potential of homocysteine as a biochemical marker for OSMF severity and progression.

In conclusion the findings of the present study demonstrate a significant elevation in serum homocysteine levels among patients with Oral Submucous Fibrosis (OSMF) compared to healthy controls, with progressively higher levels observed across increasing clinical grades of the disease. The identified cut-off value of 15.90 µmol/L showed 100% sensitivity and specificity, indicating excellent diagnostic accuracy. These results underscore the potential utility of homocysteine as a reliable biochemical marker for the diagnosis and grading of OSMF. Given its known role in oxidative stress and fibrosis, elevated homocysteine may not only reflect disease severity but also contribute to the pathogenic mechanisms underlying OSMF and its malignant transformation. Further longitudinal and interventional studies are warranted to validate homocysteine's prognostic value and its role in therapeutic monitoring of OSMF.

Author Contribution Statement

All authors contributed equally in this study.

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