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Serum Lipid Profile And C-Reactive Protein As Predictors Of Disease Progression In Oral Submucous Fibrosis: A Prospective Study

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Abstract:
Background*: Oral submucous fibrosis (OSF) is a long-standing, debilitating premalignant disease of the oral mucosa, widely prevalent in the Indian subcontinent and affecting millions across the globe. While existing studies have examined serum lipid profile and C-reactive protein in potentially malignant disorders and oral squamous cell carcinoma, comparative data on their pre- and post-treatment levels in oral conditions remain unavailable. The present prospective study evaluated the utility of serum lipid profile parameters and CRP as prognostic biomarkers across the clinical stages of OSF.*
Materials and Methods*: One hundred and five clinically confirmed OSF patients (Grade 1-IVa) of both genders, aged 18–60 years were enrolled. Comprehensive history-taking and oral examinations were performed. Venous blood samples (5 mL) were obtained prior to treatment commencement and upon completion of a six-week treatment regimen for biochemical analysis of serum lipid parameters and CRP.*
Results*: All serum lipid parameters (total cholesterol, triglycerides, HDL, LDL, VLDL) showed statistically significant post-treatment increases ($p<0.05$). CRP levels also showed a significant post-treatment decrease ($P<0.05$), along with statistically significant improvements in mouth opening and VAS pain scores across the cohort.*
Conclusion: *Serum lipid profile parameters and C-reactive protein demonstrated significant improvement following treatment, indicating their potential utility as prognostic biomarkers in oral submucous fibrosis. These findings, along with clinical improvements in mouth opening and pain, suggest that biochemical markers can aid in monitoring disease progression and therapeutic response in OSF patients*
Keywords: *C-reactive protein; lipid profile; oral submucous fibrosis; potentially malignant disorders; biomarkers; prognostic markers*

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I. Introduction

Oral submucous fibrosis (OSF) is a chronic, progressive, and potentially malignant disorder of the oral mucosa characterized by fibrosis of the submucosal tissues, leading to restricted mouth opening and functional impairment. The condition is often preceded by episodes of vesicle formation and is consistently associated with a juxta-epithelial inflammatory reaction. Over time, this results in fibroelastic remodeling of the lamina propria, epithelial atrophy, progressive mucosal rigidity, trismus, and difficulty in mastication.[1]

OSF is a condition of global concern, though its burden is disproportionately concentrated in South and Southeast Asia, where areca nut frequently consumed in preparations such as pan masala, betel quid, and gutka is deeply embedded in sociocultural practices.[2] Epidemiological data indicate a prevalence of up to 0.4% in rural Indian populations[3], while systematic reviews and meta-analyses have reported a malignant transformation rate of 7-13% in longitudinal cohorts.[4] These findings underscore the classification of oral submucous fibrosis (OSF) as a high-risk precancerous condition that necessitates rigorous surveillance and monitoring. Furthermore, India reports over 100,000 new cases of oral cancer annually[5], a substantial proportion of which are preceded by OSF, highlighting its significant role in oral carcinogenesis. Quality-of-life studies demonstrate that OSF profoundly impairs eating, speech, and social functioning, with progressive trismus representing the most debilitating functional sequelae.[6]

The aetiology of OSF is multifactorial, with habitual areca nut chewing identified as the primary cause. Its bioactive components particularly arecoline, copper, and polyphenols, affect matrix metalloproteinases, lysyl oxidase (LOX), collagenases, and pro-fibrotic cytokines such as TGF-β1, disrupting normal collagen turnover and leading to pathological fibrosis.[2] At the cellular level, arecoline induces mitochondrial reactive oxygen species, activates latent TGF-β1, and promotes fibroblast-to-myofibroblast differentiation, resulting in excessive extracellular matrix deposition in advanced OSF.[7]

Dysregulated lipid metabolism is well documented in neoplastic and preneoplastic conditions. Increased lipid demand for membrane biosynthesis during premalignant proliferation often leads to reduced serum levels of total cholesterol (TC), lipoproteins, and triglycerides (TG)[8] A 2025 systematic review and meta-analysis by Gupta et al., including 36 studies and 27 pooled datasets, demonstrated significant reductions in VLDL, LDL, HDL, TG, and TC in OSF patients compared with healthy controls.[9] A meta-analysis further showed greater lipid depletion in OSCC than in OPMDs, indicating a progressive lipolytic gradient from premalignancy to malignancy.[10] Mechanistically, this is attributed to increased sequestration and utilization of circulating lipids by metabolically active fibrotic and dysplastic cells for membrane synthesis and energy.[11]

C-reactive protein (CRP), an acute-phase reactant produced mainly by hepatocytes in response to pro-inflammatory cytokines, especially interleukin-6 (IL-6) has emerged as a useful surrogate marker of the chronic inflammation underlying OSF pathogenesis and malignant progression. Elevated serum CRP levels have been reported in both OSF and OSCC compared with healthy individuals[5,12], reflecting systemic inflammation due to areca nut-induced mucosal injury. Notably, CRP is a practical monitoring biomarker, as it is cost-effective, minimally invasive, easily repeatable, and reliably measurable using standard automated laboratory methods.[5]

Despite extensive research comparing lipid profiles and CRP levels in OSF patients with healthy controls, no study has systematically evaluated these biomarkers within the same cohort before and after a standardized treatment protocol. Such a paired longitudinal approach is crucial to establish true prognostic value by assessing not only disease association but also treatment response. Accordingly, the present study aims to: (i) assess serum lipid parameters (TC, LDL, HDL, VLDL, TG) and CRP across different clinical stages of OSF; and (ii) correlate post-treatment changes in these biomarkers with objective improvements in mouth opening and pain scores.

II. Material And Methods

This retrospective hospital-based study was conducted in the Department of Oral Medicine and Radiology, SCB Dental College and Hospital, Cuttack, Odisha, India.

Study Design: Hospital-based, prospective study

Study Location: Department of Oral Medicine and Radiology, SCB Dental College and Hospital, Cuttack, Odisha, India,

Study Duration: January 2025 to December 2025

Sample size: 105 patients with OSF.

Sample size calculation: Sample size was calculated using the formula for a paired t-test design based on a mean CRP of 3.62 ± 1.02 mg/dL in OSMF patients and a previously reported SD of differences of ~2.5 mg/L from comparable prospective studies.[12,13] Assuming a minimum detectable difference of 1.0 mg/L, $\alpha = 0.05$, and power of 80-90%, an initial estimate of 85 subjects was obtained. Adjusting for a 15–20% dropout rate and accounting for multiple lipid parameters (Total Cholesterol, LDL, HDL, TG, VLDL, and CRP) as co-primary outcomes, a final sample size of 105 was considered adequate to ensure sufficient statistical power for all planned analyses**.**

Subjects & selection method: A consecutive sampling method was used to recruit patients. Institutional ethical clearance was obtained prior to commencement (Ref. No. IEC/SCBDCH/261/2024), and written informed consent was secured from all enrolees. Ethical approval was obtained from the Institutional Review Committee (IEC/SCBDCH/261/2024). All participants were staged according to the Khanna et al.[14] classification system for OSF, which stratifies disease severity based on inter-incisal mouth opening, mucosal pliability, and the extent of fibrotic band formation. This four-stage system was selected for its widespread clinical applicability and its established correlation with histopathological severity

Inclusion criteria: Clinically diagnosed OSF patients at Stages I-IVa, of either sex, aged 18-60 years

Exclusion criteria: Patients were excluded if they presented with co-morbidities known to independently alter lipid metabolism or CRP levels, including obesity, thyroid dysfunction, diabetes mellitus, malabsorption syndromes, cardiac conditions, hepatic disease, autoimmune collagen disorders, osteomyelitis, inflammatory bowel disease, tuberculosis, active malignancy, severe systemic infection, pregnancy, oral contraceptive use, or any prior OSF treatment. These rigorous exclusion criteria were applied to minimise confounding and safeguard the internal validity of biochemical comparisons

Procedure methodology

- **Clinical Parameter Assessment**: Symptomatic pain and burning sensation were quantified on a standard 10 cm visual analog scale (VAS). Functional mouth opening was determined by measuring the maximum inter-incisal distance with a Vernier caliper in millimetres. All assessments were performed at baseline and at the conclusion of the six-week treatment course. The study followed a structured, multi-phase data collection protocol. Initially, detailed patient histories were obtained, followed by research-specific clinical examinations, including measurement of mouth opening, and subsequent clinical staging of the disease. Blood samples were then collected for biochemical analysis of serum lipid profile and C-reactive protein (CRP), along with assessment of burning sensation using a visual analogue scale (VAS). Participants were treated with intralesional dexamethasone and supportive medications, after which repeat biochemical evaluations of lipid profile and CRP levels were performed following six weeks of intervention to assess treatment response.
- **Treatment Protocol:** Grade I patients received antioxidant capsules (twice daily), vitamin B-complex tablets (twice daily), and topical 20% benzocaine gel before meals for six weeks. Grades II, III, and IVa additionally received intralesional injections of dexamethasone (2 mL) with lignocaine (0.5 mL) twice weekly for six weeks. Intralesional corticosteroids are the most widely implemented pharmacological intervention for moderate-to-severe OSF, with dexamethasone and triamcinolone diacetate being the most commonly utilised agents in the immunomodulatory studies in OSF.[15] The Cochrane review by Sridharan et al. (2024) found moderate-certainty evidence that antioxidants improve mouth opening and burning sensation VAS scores at three to six months[16], supporting the antioxidant supplementation component of the current regimen. Follow-up was weekly for Grade I and biweekly for Grades II-IVa.
- **Biochemical Analysis:** Venous blood samples (5 mL) were collected at two time points: immediately before treatment initiation and six weeks after treatment completion. The blood was allowed to clot upright for at least 20 minutes before centrifugation at 3000 rpm for 10 minutes. The resulting clear, non-haemolysed serum was then carefully separated and transferred into sterile vials for biochemical analysis. Serum lipid parameters were assessed using standard biochemical methods: total cholesterol by the cholesterol oxidase–peroxidase (CHOD-POD) method, triglycerides by the glycerol phosphate oxidase–peroxidase (GPO-POD) method, and HDL cholesterol via selective precipitation or homogeneous enzymatic techniques. LDL cholesterol was calculated using the Friedewald formula when triglyceride levels were below 400 mg/dL. All measurements were performed photometrically, with concentrations determined by comparison against standard calibrators. All sample processing and analysis were conducted in the Department of Biochemistry at S.C.B. Medical College and Hospital, Cuttack, Odisha.

Statistical analysis

Data were organized in Microsoft Excel and analyzed using SPSS Version 29 (IBM Corp., 2023). Descriptive statistics were calculated, including mean and standard deviation for continuous variables and frequencies for categorical data. Normality was assessed using the Shapiro–Wilk test, and as the data were normally distributed, Student's t-test was applied for intergroup comparisons while paired t-test was used for intragroup comparisons. A p-value of <0.05 was considered statistically significant.

III. Result

Participants ranged from 18 to 60 years of age (mean: 34.80±9.66 years). Majority of the participants were males (93; 88.5%).

Table no 1: Demographic distribution of study participants

Gender	N (%)	Mean age	P value
Males	93 988.5%)	34.93±10.04	0. 671 (NS)
Females	12 (11.5%)	33.75±5.93	0.225 (NS)

Table no 2: Mean age of study participants according to OSMF grading

Group	N (%)	Mean age
Grade I	33 (31.43%)	33.36±5.22
Grade II	27 (25.71%)	33.88±13.53
Grade III	39 (37.14%)	35.46±9.00
Grade IVa	6 (5.71%)	42.5±7.5
Total	105 (100%)	38.40±9.67

Table 2 represents the distribution and mean age of the study participants across OSMF grades. Grade III accounted for the largest group with 39 subjects (37.14%), showing a mean age of 35.46±9.00 years where as grade IV had the fewest participants (6; 5.71%) and the highest mean age of 42.50±7.50 years. Overall, a progressive increase in mean age was observed with advancing OSMF severity

Table no 3: Comparison of pre-treatment and post-treatment mean (±SD) values of lipid profile and CRP of the overall study subjects

Parameters	Pre-treatment (Mean±SD)	Post-treatment (Mean±SD)	P value
Total Cholesterol	154.12± 35.71	174.74±32.62	<0.001*
Triglycerides	142.24±76.47	188.97±69.79	<0.001*
High Density Lipoprotein	38.82±7.62	44.02±7.47	<0.001*
Low Density Lipoprotein	101.78±28.26	118.28±26.24	0.001*
Very Low-Density Lipoprotein	28.19±11.17	34.28±8.72	0.001*
C-reactive protein	8.82±6.29	4.28±4.02	<0.001*
Student t test; p<0.05 *			

Table 3 presents a comparative analysis of pre- and post-treatment mean (±SD) values for lipid profile parameters and CRP across the overall study cohort. Statistical evaluation revealed significant alterations across all measured parameters following treatment.

Total cholesterol exhibited a statistically significant increase of approximately 13.4%, rising from 154.12 ± 35.71 mg/dL to 174.74 ± 32.62 mg/dL (p<0.001), while triglycerides demonstrated the most pronounced elevation at 32.9%, from 142.24 ± 76.47 mg/dL to 188.97 ± 69.79 mg/dL (p<0.001). Among lipoprotein fractions, HDL, LDL, and VLDL all recorded statistically significant post-treatment increases of 13.4%, 12.8% and 19.3% (all, p<0.05), respectively.

In contrast, CRP, a key marker of systemic inflammation, followed a divergent pattern, registering a significant decline of approximately 51.5%, from 8.82 ± 6.29 mg/L to 4.28 ± 4.02 mg/L (p<0.001), suggesting a meaningful anti-inflammatory effect of the treatment despite the concurrent elevation in lipid parameters.

Table no 4: Stage-wise comparison of pre- and post-treatment mouth opening and VAS scores

Stage	Mouth opening (Pre)	Mouth opening (Post)	P value	VAS (Pre)	VAS (Post)	P value
I	38.18±2.24	40.27±1.50	0.000*	4.54±1.00	2.27±1.15	0.000*
II	31.44±3.08	34.33±3.32	0.000*	4.77±1.71	1.77±1.96	0.000*
III	25.86±3.50	30.30±3.35	0.000*	6.53±1.51	3.61±1.56	0.000*
IVa	14.50±0.54	18.83±0.40	0.000*	4.83±0.04	2.00±1.09	0.000*
Overall	30.71±7.27	33.82±6.14	0.001*	5.37±1.60	2.62±1.70	0.000*
Paired t test; p<0.05 *; VAS = Visual Analog Scale.						

Table 4 presents a comparative analysis of pre- and post-treatment mean (±SD) values for mouth opening and VAS scores stratified by OSMF grade. Statistically significant improvements were observed across all grades for both parameters.

Regarding mouth opening, improvements followed a grade-dependent pattern, with the most severe cases demonstrating the greatest absolute gains. Grade I, II, III, and IV patients recorded increases of 2.09 mm (p<0.0001), 2.89 mm (p=0.001), 4.44 mm (p<0.0001), and 4.33 mm (p<0.0001), respectively. Overall, mean mouth opening improved from 30.71±7.27 mm to 33.82±6.14 mm (p=0.001), affirming treatment efficacy across all severity levels.

A parallel trend was observed in VAS scores, where all grades exhibited significant reductions in pain and burning sensation in all the grades from baseline. The overall mean VAS score declined markedly from 5.37±1.60 to 2.62±1.70 (p<0.0001), underscoring the treatment's consistent symptomatic efficacy across all OSMF grades.

Table no 5: Stage-wise comparison of pre- and post-treatment serum lipid profile and C-reactive protein

Grade	I	II	III	IVa	Overall
Serum cholesterol					
Pre	181.51±44.37	151.88±20.74	138.51±20.53	115.00±4.38	154.12± 35.71
Post	204.81±32.17	170.77±19.70	158.38±21.21	133.50±10.40	174.74±32.62
P value	0.017*	0.0012*	0.000*	0.002*	0.000*
Serum triglycerides					
Pre	176.69±102.94	120.92±39.84	137.35±64.31	80.50±15.88	142.24±76.47
Post	247.90±73.08	158.33±36.04	166.53±54.66	148.5±69.02	188.97±69.79
P value	0.000*	0.000*	0.03*	0.04*	0.000*
High density lipoprotein (HDL)					
Pre	41.09±6.53	41.66±5.88	34.92±7.90	39.00±9.85	38.82±7.62
Post	44.18±5.82	46.44±6.87	42.15±8.89	44.50±7.12	44.02±7.47
P value	0.04*	0.008*	0.003*	0.02*	0.000*
Serum low density lipoprotein (LDL)					
Pre	110.54±34.34	99.40±22.70	99.64±24.89	78.16±24.44	101.78±28.26
Post	128.36±25.45	115.00±21.13	114.92±29.67	99.50±8.21	118.28±26.24
P value	0.01*	0.01*	0.01*	0.07	0.001*

Serum very low density lipoprotein (VLDL)					
Pre	35.33±10.54	29.77±6.65	21.53±9.85	25.00±15.33	28.19±11.17
Post	41.18±7.55	33.33±4.32	29.30±8.11	33.00±10.95	34.28±8.72
P value	0.01*	0.02*	0.003*	0.32	0.001*
Serum C-reactive protein (CRP)					
Pre	9.58±5.13	11.97±7.66	6.66±5.38	4.50±3.83	8.82±6.26
Post	4.52±3.51	5.78±5.80	3.24±2.74	3.00±2.19	4.28±4.02
P value	0.000*	0.000*	0.000*	0.42	0.000*
Paired Student's t-test; * Statistically significant ($p < 0.05$).					

Table 5 compares pre- and post-treatment serum lipid profiles and C-reactive protein (CRP) across four disease grades (I-IVa), with an overall column. All parameters show statistically significant changes ($p<0.05$) after treatment in the overall group. Serum cholesterol levels increased post-treatment across all grades. The rise was most pronounced in Grade I (181.51 to 204.81 mg/dL), and all comparisons were statistically significant. Lower-grade patients had higher baseline cholesterol, suggesting the condition's severity inversely correlates with cholesterol levels. All grades reached significance, indicating consistent triglyceride elevation post-treatment. A favorable rise in HDL was observed across all grades post-treatment. Similarly, LDL increased post-treatment in all grades. Notably, Grade IV did not reach statistical significance ($p=0.07$), possibly due to the small sample or high variability (99.50±8.21). Overall significance ($p=0.001$) confirms a consistent trend. For VLDL, increases were seen across grades, but Grade IVa did not achieve significance ($p=0.32$). All other grades and the overall comparison were significant. On the contrary to serum lipid profile paramaters, C-reactive protein showed a decreased post-treatment, indicating reduced systemic inflammation. Grade I showed the greatest decrease (9.58 to 4.52 mg/L). Grades I–III showed highly significant reductions ($p=0.000$), while Grade IV did not reach significance ($p=0.42$), likely due to already low baseline values and small sample size.

IV. Discussion

Head and neck cancer is a major cause of morbidity and mortality worldwide, with oral cancer ranking as the sixth most common cancer globally. Approximately 90% of oral cancer cases are attributed to tobacco consumption. Although malignant transformation represents the final and most aggressive stage of oncogenesis, the progression to cancer typically begins much earlier. Therefore, the identification and characterization of premalignant or precancerous conditions are of paramount importance, as these intermediate stages offer a critical window for early detection, timely therapeutic intervention, and the implementation of preventive strategies to reduce the risk of progression to invasive oral carcinoma. Biochemical markers offer significant advantages as they are simple, minimally invasive, cost-effective, and easy to interpret.

Demographic Observations

The mean age observed in the OSMF group in the present study was consistent with existing literature, which reported that OSMF commonly affects individuals in the third to fourth decades of life. Several studies report similar mean ages in OSMF patients, with Rajendran *et al*[17]noting a range of 30-40 years and Tilakaratne *et al*.[15] observing a predominance in young adults, while Patel *et al*.[18] and Metgud *et al*.[19] reported mean ages in the mid-thirties, consistent with the present findings. However, increased accessibility and early initiation of these habits had resulted in a noticeable shift of OSMF toward a younger population in recent decades highlighting its significant public health impact.[20]

The strong male preponderance in this cohort (96.6%) is consistent with earlier epidemiological reports. Rawson et al.[21] and Baduni et al.[22] documented approximately 95% male predominance in their respective OSF populations. This pattern predominantly reflects higher rates of areca nut chewing among males in South Asian communities. However, the growing availability of flavoured areca nut products marketed towards younger demographics and females suggests that the gender distribution of OSF may narrow in future studies, an observation echoed in contemporary OSF reviews.[2]

In the current study disease severity increased with advancing age, likely reflecting prolonged exposure to etiological factors such as areca nut and gutkha chewing. The predominance of Stage III cases in the present study may be attributed to delay in reporting, poor early symptom recognition, and limited disease awareness among the general population. The progressive increase in mean age across grades aligns with previous studies, where Pindborg *et al*.[23] and Rajendran *et al*.[17] reported that advanced OSMF is more common in older individuals with prolonged areca nut use. Similarly, Tilakaratne *et al*.[15] and Murti *et al*.[24] noted that severe fibrosis and trismus are typically seen in older patients, emphasizing the role of chronicity and cumulative exposure in disease progression.

Clinical Outcomes: Mouth Opening

The pre- and post-treatment analysis of mouth opening in OSMF patients showed a statistically significant improvement across all disease grades. This positive clinical response can be attributed to reduction in inflammation, partial reversal of fibrosis, improved mucosal elasticity, and enhanced muscle function following treatment. The mean net gain in inter-incisal distance of 3.11±0.93 mm is clinically meaningful, given that inter-incisal distances below 30 mm are widely regarded as the threshold necessitating active intervention.[15] These findings are consistent with previous investigators. Pindborg *et al*.[23] reported modest but significant improvement in mouth opening following medical management, particularly in early and moderate stages. Rajendran et al.[17] observed better treatment response in early stages with limited but meaningful improvement in advanced cases. Tilakaratne *et al*.[15] confirmed that mouth opening is a reliable clinical indicator of treatment response. Gupta *et al*.[25] and Borle and Borle *et al*.[26] documented significant increases following intralesional steroid therapy and habit cessation. Haider *et al*.[27]and Warnakulasuriya *et al*.[28] confirmed that multimodal approaches, including antioxidants, physiotherapy, and pharmacological agents, lead to significant improvement. Similar findings were reported by Kumar *et al*.[29] and Maher *et al*.[30] Importantly, improvement in mouth opening correlated with simultaneous biochemical improvements in lipid profile and CRP, suggesting that reduced systemic inflammation contributes to improved tissue remodeling and functional recovery

A recent Cochrane systematic review found moderate-certainty evidence that antioxidants improve mouth opening at three to six months and noted very uncertain evidence for intralesional dexamethasone alone on mouth opening, highlighting the benefit of the combination regimen employed in the present study.[16]

Pain and Burning Sensation

VAS scores showed a highly statistically significant reduction across all OSMF grades, with the overall mean decreasing from 5.37±1.60 to 2.62±1.70 post-treatment ($p<0.0001$), indicating substantial symptomatic improvement. Burning sensation in OSMF is primarily attributed to epithelial atrophy, chronic inflammation, reduced salivary protection, and increased exposure of nerve endings; areca nut-induced mucosal injury perpetuates these changes through release of pro-inflammatory mediators and mucosal hypersensitivity. Therapeutic interventions targeting inflammation and epithelial integrity are therefore expected to yield symptomatic relief as reflected in reduced VAS scores.

These findings align with prior studies. Pindborg *et al*.[23] identified burning sensation reduction as one of the earliest and most consistent indicators of therapeutic response, while Rajendran *et al*.[17] observed that symptomatic improvement often precedes measurable changes in mouth opening, highlighting the sensitivity of VAS assessment. Tilakaratne *et al*.[15] emphasized burning sensation as a major patient-reported outcome measure showing significant improvement following medical management and habit cessation. Borle and Borle *et al*.[26] demonstrated significant VAS reduction after intralesional corticosteroid therapy, and Gupta *et al*.[25] and Haider *et al*.[27] reported marked improvement following multimodal treatment. Warnakulasuriya *et al*.[28] highlighted that VAS improvement significantly enhances patient compliance and quality of life. The significant VAS reduction also correlated with decreased CRP levels, supporting the hypothesis that burning sensation in OSMF is closely linked to inflammatory activity rather than fibrosis alone.[16]

Total Cholesterol

Serum cholesterol levels showed a statistically significant increase across all OSMF grades following treatment, with the overall mean rising from 154.12±35.71 mg/dL to 174.74±32.62 mg/dL ($p=0.0001$). Pre-treatment hypolipidemia in OSMF reflects enhanced lipid peroxidation, increased cholesterol utilization during heightened epithelial turnover, and suppression of hepatic cholesterol synthesis by pro-inflammatory cytokines (IL-6, TNF-α). The significant post-treatment increase suggests partial reversal of these disease-related metabolic alterations, driven by reduced inflammatory burden and decreased oxidative cholesterol degradation.

These findings are consistent with multiple studies reported in literaure. Studies by Patel *et al*.,[18] Mehrotra *et al*.,[11] and others[18,31-35] reported significantly lower cholesterol in OSMF and oral leukoplakia patients compared to controls, with progressive decline in advanced stages, and demonstrated reversibility following treatment and habit cessation. Sharma *et al*.[36] additionally noted concurrent decreases in both TC and LDL in OSF patients. The grade-wise trend supports the role of serum cholesterol as a marker of disease severity. Furthermore, since cholesterol is essential for membrane integrity and cell signaling, its restoration post-treatment may reflect improved cellular homeostasis and reduced susceptibility to carcinogenic penetration.

Triglycerides

Serum triglyceride (TG) levels increased significantly across all grades following treatment, with the overall mean rising from 142.24±76.47 mg/dL to 188.97±69.79 mg/dL ($p<0.001$).

Pre-treatment hypotriglyceridemia in OSMF is explained by increased oxidative stress and lipid peroxidation, elevated TNF-α and IL-6 suppressing hepatic lipoprotein synthesis, and enhanced utilization of circulating triglycerides during active epithelial repair. The significant post-treatment increase reflects partial restoration of hepatic lipid metabolism following reduction in inflammation, cessation or reduction of areca nut exposure, and improved tissue remodeling. Notably, Grade IVa patients demonstrated the largest relative increase despite the lowest baseline values, suggesting that even advanced OSMF retains metabolic responsiveness to intervention.

These findings are supported by Mehrotra *et al*.,[11] Patel *et al*.,[18] Gupta *et al*.,[25] and Ajai *et al*.,[33] who reported that TG levels are inversely related to OSMF severity and improve following anti-inflammatory therapy and habit cessation. Restoration of normal lipid turnover following reduction in hyperactive collagen metabolism plausibly accounts for post-treatment TG elevation. From a molecular standpoint, TG-rich VLDL particles supply fatty acids for membrane phospholipid synthesis in proliferating cells[10]; normalisation of TG concentrations therefore signifies abatement of this metabolic demand.

High-Density Lipoprotein

HDL levels increased significantly across all OSMF grades following treatment, with the overall mean rising from 38.82±7.62 mg/dL to 44.02±7.47 mg/dL ($p<0.001$). Pre-treatment reduction in HDL is attributed to oxidative modification and functional impairment of HDL particles during chronic inflammation, as well as suppression of apolipoprotein A1 production by IL-6 and TNF-α. The significant post-treatment increase suggests that reduction in inflammatory burden restores HDL synthesis and function, thereby enhancing reverse cholesterol transport, reducing oxidative stress, and providing protective effects to the oral mucosa. The marked improvement in Grades III and IVa patients indicates that even advanced OSMF retains capacity for metabolic recovery.

These findings are corroborated by Patel *et al*.,[18] who reported significant post-treatment HDL elevation correlating with symptomatic improvement, and Gupta *et al*.,[25] who observed HDL improvement following areca nut cessation and medical management. Goel *et al*.[31] emphasized that low HDL in oral premalignant conditions reflects oxidative stress and disease severity, with post-treatment restoration indicating improved antioxidant defense. Similar findings were reported by Ajai *et al*.,[33] Mehrotra *et al*.,[52] and Lohe *et al*.[11] Post-treatment restoration of HDL carries additional cardiometabolic significance, given HDL's roles in reverse cholesterol transport and anti-inflammatory signaling.

Low-Density Lipoprotein

Serum LDL levels increased significantly overall following treatment, with the mean rising from 101.78±28.26 mg/dL to 118.28±26.24 mg/dL ($p=0.001$). Pre-treatment LDL reduction in OSMF reflects disease-induced hypolipidemia. LDL serves as a critical cholesterol source for cellular repair during active epithelial turnover, and its depletion indicates ongoing metabolic stress. The significant post-treatment increase in early and moderate grades reflects restoration of lipid homeostasis through reduced systemic inflammation, improved mucosal vascularity, and partial reversal of fibrotic changes. The relatively modest and non-significant increase in Grade IVa patients likely reflects irreversible metabolic compromise from extensive fibrosis and persistent oxidative stress, compounded by the small sample size (n=6).

Patel *et al*.[18]and Gupta *et al*.[25] reported significant LDL improvement following habit cessation and therapeutic intervention in oral premalignant disorders. Goel *et al*.,[31] Sai *et al*.,[32] and Metgud *et al*.[19] confirmed that LDL levels correlate inversely with disease severity and improve following treatment. Sharma *et al*.[36] and Kanthem *et al*.[37] also observed significant decreases in serum cholesterol and LDL in OSF patients. Persistent low LDL despite treatment may suggest ongoing inflammatory activity or higher risk of disease progression.

Very Low-Density Lipoprotein

Serum VLDL levels rose significantly overall following treatment, with the mean increasing from 28.19±11.17 mg/dL to 34.28±8.72 mg/dL ($p=0.001$). Pre-treatment VLDL reduction in OSMF is consistent with the effect of chronic inflammatory cytokines (TNF-α, IL-6) impairing hepatic triglyceride synthesis and transport, and increasing catabolism. The post-treatment increase across most grades reflects restoration of hepatic lipid metabolism and reduction of inflammatory burden; Grade III patients exhibited the highest relative increase from the lowest baseline, highlighting sustained metabolic responsiveness even in severe disease. The non-significant increase in Grade IVa likely reflects persistent fibrosis and metabolic compromise.

Patel *et al*.18 and Gupta *et al*.[25] reported VLDL improvement following treatment and habit cessation in oral premalignant disorders. Goel et al.[31] emphasized that low VLDL is a marker of active disease, with post-treatment increases indicating reversal of disease-induced hypolipidemia. Rawson *et al*.[21] and Anusha *et al*.[38] also observed significantly decreased VLDL in OSF patients compared to controls, consistent with the present findings. The convergent directional changes across all five lipid fractions, uniformly depressed before

treatment and restored to higher levels post-treatment, collectively and compellingly support the interpretation that active OSF imposes a state of heightened systemic lipid demand that normalises as the disease responds to therapy.

C-Reactive Protein

In contrast to lipid parameters, CRP levels showed a statistically significant reduction across most OSMF grades following treatment, with the overall mean decreasing from 8.82±6.26 mg/L to 4.28±4.02 mg/L (p=0.001). This trajectory reflects the inflammatory burden imposed by active OSF and its attenuation with treatment. Bhattacharjee *et al*.[39] similarly documented elevated CRP in both leukoplakia and OSF relative to healthy individuals. A cross-sectional study by Gosavi and Torkadi *et al*.,[5] involving 150 participants divided equally into healthy, OSF, and OSCC groups demonstrated a stepwise CRP elevation from controls to OSF to OSCC, suggesting that CRP tracks inflammatory disease burden across the premalignant-to-malignant continuum. Kiran *et al*. further confirmed significantly higher CRP levels in OSF patients (3.62±1.02 mg/dL) compared with healthy controls (0.40±0.21 mg/dL), all of whom were long-term areca nut consumers[12], corroborating the aetiological link between areca nut-induced mucosal inflammation and systemic CRP elevation.

The reduction in CRP following combined corticosteroid and antioxidant therapy in the present study is mechanistically coherent: intralesional corticosteroids suppress TGF-β1 and downstream pro-inflammatory mediators[40], while antioxidants attenuate reactive oxygen species (ROS)-mediated NF-κB activation, together reducing the hepatic stimulus for CRP synthesis.[7] As a sensitive acute-phase reactant, elevated pre-treatment CRP reflects the chronic inflammatory environment driven by areca nut-induced epithelial injury, mucosal atrophy, and oxidative stress, mediated by IL-6 and TNF-α stimulating hepatic CRP synthesis. The significant post-treatment reduction indicates successful suppression of systemic inflammatory activity through medical intervention, habit cessation, and reduction in mucosal injury. Notably, CRP levels were highest in early and moderate stages (Grades I-III), where active inflammation predominates, while Grade IVa showed lower baseline CRP, consistent with the understanding that CRP reflects active inflammatory processes rather than established fibrosis. Persistent CRP elevation despite therapy may indicate subclinical inflammation, poor treatment response, or higher malignant potential, warranting closer clinical surveillance.

Strengths, Limitations, and Future Directions

The major strengths of this study include its comprehensive multidimensional evaluation incorporating both biochemical markers (serum lipid profile and CRP) and clinical parameters (mouth opening and VAS), with grade-wise analysis providing detailed insight into disease severity and its systemic associations. The pre- and post-treatment design highlights the dynamic responsiveness of these biomarkers to therapy, while a well-matched control group, standardized diagnostic criteria, and validated laboratory methods enhance internal validity.

Key limitations include the small Grade IVa sample size, limiting statistical power for advanced disease; the short-term interventional design without long-term follow-up, restricting assessment of sustained changes and malignant transformation risk; and unquantified confounders such as habit duration, nutritional status, and dietary lipid intake. Additionally, advanced inflammatory and oxidative stress markers (IL-6, TNF-α, malondialdehyde) were not evaluated, which could have provided deeper mechanistic insight into the inflammation–lipid dysregulation axis in OSMF.

V. Conclusion

The present study establishes a consistent, statistically significant inverse relationship between serum lipid profile parameters and OSF disease activity before treatment, with restoration of all five lipid fractions observed post-treatment as clinical improvement occurred. Concurrently, CRP, an objective marker of systemic inflammatory burden was elevated in active OSF and declined significantly following therapeutic intervention. These findings, corroborated by a rapidly accumulating body of evidence from systematic reviews and meta-analyses demonstrate that serum lipid profiling and CRP measurement possess genuine prognostic value in OSF, capable of objectively reflecting both disease severity and treatment efficacy. Their incorporation into routine OSF surveillance may facilitate earlier detection of disease progression and more nuanced monitoring of therapeutic outcomes. Larger, multi-centre longitudinal trials with inclusion of all OSF stages are warranted to validate and extend these findings.

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