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Correlation of serum protein and lipid profile with OSMF severity among the rural population of Southern India

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ABSTRACT

Background: Carcinogenesis is mostly observed due to alterations in serum protein and lipid levels.

Objectives: In this present study, serum protein and lipid profile are to be evaluated in OSMF patients and compared with various clinical stages of OSMF.

Materials and methods: Out of 100 study subjects, 45 OSMF patients were selected as cases; 55 apparently healthy individuals were chosen as controls. The level of serum total protein, albumin, and globulin; high density lipoprotein (HDL), very low density lipoprotein (VLDL), total cholesterol (TC), triglycerides (TG), and low density lipoprotein (LDL) were measured by COBAS-6000 autoanalyzer. The obtained data were processed with an independent sample t-test.

Results: Statistically significant reduction in serum total protein and albumin, LDL, HDL, TC, and TG levels were detected in all stages of OSMF patients in comparison with controls, whereas changes in serum VLDL level were not statistically significant.

Conclusion: The current study showed significant alterations in serum protein and lipid profile, with advancement in the clinical stages of OSMF. In the future, the alterations in these parameters might possess a diagnostic significance and can be utilized as a biochemical indicator for the detection of neoplastic processes like OSMF.

Introduction

Oral submucous fibrosis (OSMF) is a disabling, premalignant lesion of the buccal mucosa, with insidious onset.[1] It is predominant in India, Polynesia, Taiwan, Southern China, Sri Lanka, Pakistan, and Bangladesh.[2] In 2002, it is reported by OSMF statistics of the Indian sub-continent that near about 5 million people (a total of 0.5% of the Indian population).[3] In research, a study based on oral precancerous lesions as well as oral cancer among the rural population of India, the rate of OSMF malignant transformation, was observed to be 7.6% over 17 years.[4]

Any part of the buccal cavity, sometimes even the pharynx can be affected by OSMF. It is invariably linked with an inflammatory process of juxta epithelial cells and subsequently fibroelastic alteration of lamina propria leading to the formation of the vesicle with epithelial atrophy, causing stiffness of the buccal mucosa, which results in trismus and difficulty in chewing.[5] The significance of

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OSMF lies in the highest rate of malignant transformation and its restriction during the opening of the mouth. The prevalence of OSMF in India is found to be 0.2-0.5%, whereas the malignant transformation rate is about 7-13%.[6,7] Though the causative etiological factor of OSMF is multifactorial, areca nut possesses a pivotal role in the manifestation of the disease.[8,9] The chronic oral irritation due to chewing pan masala and gutkha causes injury, ultimately resulting in prolonged inflammation along with the production of cytokines and finally oxidative damage. Subsequent production of ROS (reactive oxygen species) along with oxidative stress can evoke cell proliferation, and cell aging and ultimately result in cell death, The whole series of events is solely dependent on the magnitude of the production of ROS.[10,11] Aside from that, protein oxidation has a crucial role in oral carcinogenesis.[12,13] Hypoproteinemia, exhibited as cachexia is often observed in oral malignancy.[14] So, the serum protein levels can be implemented as a vital prognostic, as well as, a diagnostic tool for this premalignant OSMF. Lipids are considered the cell membranes' elementary components which perform a wide spectrum of biological events such as the proliferation and growth of normal cells as well as malignant tissues.[13] Very less studies are available to date regarding the correlation of serum protein and lipid profile with the advancement of OSMF stage. Therefore, the study aims to correlate the levels of serum proteins and lipid profiles with OSMF severity.

Materials and methods

Source of Data

The current study was carried out at the Department of Biochemistry and Oral Medicine at Panineeya Institute of Dental Sciences and Research Centre, situated in Telangana, India. The study was sanctioned by Institutional Ethics Committee.

Study participants

A total of 100 subjects were chosen from the Outpatient Department of Oral Medicine for this study. The study subjects were categorized into two groups, such as the case group and the control group. The case group comprises of 45 OSMF patients and the control group of 55 age and sex-matched apparently healthy individuals. The subjects with any associated comorbidities which can affect the level of aforesaid study parameters were not included in this study. The case group was further categorized into stages I, II, III, and IV, according to their initial mouth opening as measured by inter-incisal distance.

Sample collection

After acquiring institutional ethical committee clearance, and subsequently informed written consent from every subject, a detailed clinical history was noted. After a minimum of 12 hrs fasting the study subjects were called for blood sample collection. Five mL of venous blood was collected under strict aseptic precautions. Then, the collected samples were centrifuged at 3,000 rpm for five minutes to obtain serum.

Parameters analyzed

The serum levels of TC, HDL, LDL, TG, VLDL, total protein, albumin, and globulin were analyzed using commercially available assay kits of Roche Diagnostics using Cobas 6000 autoanalyzer. The data obtained were processed using SPSS, version 20.0. Mean with the standard deviation were determined for TC, HDL, LDL, TG, VLDL, total protein, albumin, and globulin in the cases, as well as, in the control group.

Data processing

An Independent sample t-test was implemented to verify the statistical significance of mean differences. The collected data were entered into an Excel spreadsheet and analyzed using SPSS software v20.0.

Results

As mentioned formerly, A total of 100 subjects were included in the study, out of which 45 were cases and 55 were controls. As far as the clinical staging is concerned, 17 cases (37.78%) were included in Stage I, 11 cases (24.45%) in Stage II, 14 cases (31.11%) in Stage III, and 3 cases (6.66%) in Stage IV. (Table 1).

Table 1 Comparison of Baseline characteristics: number (%), age, and gender among OSMF subjects.

	Cases (N=45)	Controls (N=55)
Mean±SD	45.60±10.84	47.08±9.90
Median (IQR)	47.00 (36.5-55.0)	49.00 (41.5-55.0)
p value[#]	0.586	
Age group	**Cases N (%)**	**Controls N (%)**
<30 years	4 (8)	3 ()
30-40 years	13 (30)	10 (18)
>40 years	28 (62)	42 (76)
p value[Ω]	0.308	
Gender	**Cases N (%)**	**Controls N (%)**
Male	24 (53)	26 (47)
Female	21 (47)	29 (53)
p value[*]	0.548	
Stage of OSMF patients	**Number**	**%**
Stage I	17 (8M+9F)	37.78
Stage II	11 (7M+4F)	24.45
Stage III	14 (8M+6F)	31.11
Stage IV	3 (1M+2F)	06.66
Total	45	100

*IQR: inter-quartile range, M: male, F: female, [#]Mann-Whitney U test was used to calculate p value ,[Ω]Fischer exact test was used to calculate p value, *Chi-square test was used to calculate p value.*

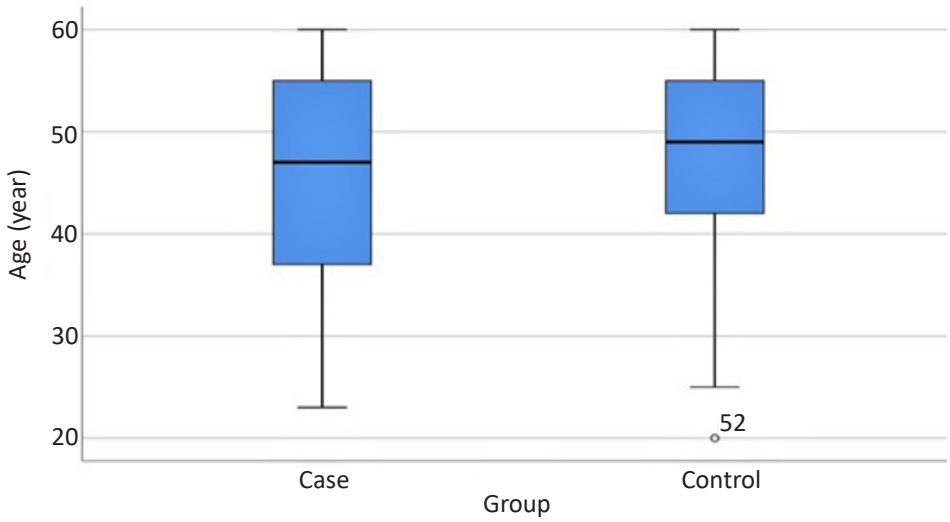

Figure 1. *Box plot showing a comparison of median age between the case and the control group.*

Table 2 represents, the mean serum total protein level (5.83±0.36 g/dL) and albumin level (3.21±0.45 g/dL) among OSMF cases, which was found to be significantly less in comparison with the total protein level (7.42±0.67 g/dL) and albumin level (4.50±0.51g/dL) in the control group, at $p<0.001$ each. But the mean serum globulin level among the cases (3.87±0.54 g/dL), was found to be raised significantly, in comparison with the control group (3.20±0.43 g/dL) at $p<0.001$. Here, p values were calculated by the Mann-Whitney U test. The mean serum total protein, albumin exhibited a decreasing trend, with the advancement of the clinical staging of OSMF. In contrast, the mean serum globulin level exhibited a reverse trend among different stages of OSMF [Table 2]. The A/G ratios were found to be 0.91±0.07, 1.04±0.21, 0.88±0.56, and 0.69±0.54 in OSMF cases, belonging to Stage I, II, III, IV respectively.

Table 2 Mean±SD of serum protein parameters (g/dL) among OSMF subjects.

Group	Total protein	Albumin	Globulin
Controls (N=55)	7.42±0.67	4.50±0.51	3.20±0.43
Cases (N=45)	5.83±0.36	3.21±0.45	3.87±0.54
p value	<0.001*	<0.001*	<0.001*
OSMF stage	**Total protein**	**Albumin**	**Globulin**
Stage I	5.98±0.56	3.42±0.57	4.13±0.31
Stage II	4.94±0.38	3.58±0.39	3.50±0.75
Stage III	5.01±1.16	3.22±1.13	3.76±1.47
Stage IV	4.89±1.58	2.90±1.46	4.38±0.98

**Significant*

Table 3 represents the mean with standard deviation (SD) and *p* value of all serum lipid parameters, those were analyzed and compared. Significantly lower levels of serum TC (156.76±20.25 mg/dL), HDL (34.16±7.06 mg/dL), and LDL (85.69±17.58 mg/dL) were observed among OSMF cases, as compared to the control group (TC=185.35±13.87 mg/dL, HDL=43.60±6.29 mg/dL, LDL=116.36±21.56 mg/dL). Statistically significant differences were observed for TC, HDL, and LDL with $p<0.001$ each. While, the mean value of serum TG (118.02±17.02 mg/dL) and VLDL (24.28±4.41mg/dL) among cases compared with controls (TG=124.44±11.01 mg/dL), and (VLDL=24.76±4.67 mg/dL), p value found to be 0.025 and 0.601 respectively, a statistically significant difference was not found in the later ($p>0.05$). Here, p values were calculated by Mann-Whitney U test (Table 3).

The mean serum Total Cholesterol, HDL and LDL levels exhibited a markedly decreasing trend along with the advancement of the clinical staging of OSMF, unlike the mean serum TG and VLDL levels. The mean serum Total Cholesterol, HDL and LDL levels exhibited a markedly decreasing trend along with the advancement of the clinical staging of OSMF, unlike the mean serum TG and VLDL levels (Table 3).

Table 3 Mean±SD of serum lipid parameters (mg/dL) among OSMF subjects.

Group	Total protein	Triglyceride	HDL	LDL	VLDL
Controls (N=55)	185.35±13.87	124.44±11.01	43.60±6.29	116.36±21.56	24.76±4.67
Cases (N=45)	156.76±20.25	118.02±17.02	34.16±7.06	85.69±17.58	24.28±4.41
p value	<0.001*	0.025*	<0.001*	<0.001*	0.601†
OSMF stage	**Total protein**	**Triglyceride**	**HDL**	**LDL**	**VLDL**
Stage I	159.39±9.13	36.63±3.34	98.38±9.91	119.7±17.33	33.22±2.93
Stage II	160.38±6.07	36.94±3.89	98.39±4.87	129.26±10.64	25.07±1.93
Stage III	147.60±10.55	38.98±3.44	85.32±19.19	141.91±35.12	28.32±7.01
Stage IV	145.93±6.47	32.85±3.27	84.52±3.94	140.69±19.73	28.26±4.10

**significant, †not significant, HDL: high density lipoproteins, LDL: low density lipoproteins, VLDL: very low density lipoproteins.*

Discussion

The fragmented molecule with one or more unpaired electrons and having the capacity of independent existence is termed a free radical. At a higher concentration, free radicals interact with macromolecules at intracellular levels like lipids, carbohydrates, proteins, and DNA which initiates carcinogenesis as well as inflammation.[15] During the pathogenesis of cancer, an important role is played by protein oxidation as seen in the case of premalignant OSMF, the protein level is decreased.[12,13] In oral cancer, free radicals play a vital role as an etiological factor that damage's the tissues and such damage is accentuated by the regular habit of areca nut and tobacco. Such habits are rampant among Asians, irrespective of age and sex.

In our present study, low serum protein level among OSMF cases is observed, which is statistically significant. Similar findings were observed by Patidar *et al*, Rajendran *et al*., and Dawood *et al*. among cases and controls, whereas Chandran *et al*. study findings differ from our result. [13,16-18] In oral malignancy, the rise in the level of serum protein levels may be due to inflammatory reactions.

Comparing on the intergroup basis for the level of serum albumin, a statistically significant (p>0.05) value was found and our study result was in accordance with Singh *et al*. Nayyar *et al*. Chandran *et al*. and Rajendran *et al*.[12-14, 17] While the rise in the level of serum globulin among OSMF cases can be attributed to the action of acute phase reactant and our study is in concordance with Dawood *et al*.[18]

Lipids are the major and essential components of a cell membrane that has different biological functions such as maintaining the functional and structural integrity of all biological membranes, as well as supporting in division and growth of the cell that may be a malignant or normal tissue.[19] Many studies have proved that various esophageal, as well as head and neck cancer, are directly associated with lowered blood lipid levels.[20-24,19] Researchers have observed that with a lower level of serum cholesterol, there is a high risk of cancer and mortality.[25,26] The inverse association of the incidence of cancer and cholesterol concentrations can be explained by three major competing hypotheses such hypothesis one states that before the detection or manifestation of cancer or during the process of cancer low cholesterol value is observed. Another hypothesis suggests that the association of low cholesterol value with cancer is secondary indicating that cholesterol serves as a marker for some other causal variable or set of variables, and the third hypothesis suggests cholesterol values may be decreased preceding the development of cancer and can be causally associated with its occurrence.[19,26] LDL and HDL, are those lipoproteins containing, Cholesterol is an important constituent. Most of the cholesterol is transported in the form of LDL. LDL, the fraction of lipoproteins gets restored in the human body cells as cholesterol. For circulating and metabolizing the LDL level, there is always a requirement for LDL receptors. In order to lower the serum cholesterol level, the high activity of the LDL receptors is essential. In the current study, it is observed, the patients suffering from OSMF have a significant decrease in LDL and serum cholesterol levels, this may be due to the effect of a disease that is based on cholesterol utilization for membrane biogenesis.

Conclusion

The current study demonstrates the presence of an inverse relationship between serum proteins (total protein and albumin) and serum lipids (total cholesterol, HDL, and LDL) with the oral precancerous state of OSMF. The initial development that arises in the neoplastic cells can be studied from the status of reduced serum protein and lipid levels, which can be used as a marker or indicator. The difference in lipid and protein levels may be applied as a diagnostic or prognostic biochemical marker of malignant and premalignant oral lesions.

Limitations

The current study findings are limited to a small-scale population, so in order to validate the study the sample size may be increased or may be conducted with a large population. An advanced and in-depth study on the alteration of serum protein and lipid levels can be carried out by taking various cancerous and precancerous lesions among a larger population. Correlation with epithelial dysplasia has not been included in the present study.

Conflict of interest

Nil

Funding Source:

Nil

Ethical Approval:

The study has been approved by IEC of Panineeya Institute of Dental Sciences and Research Centre with approval number PMVIDS&RC/IEC/PHD/PR/0064-15.

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References

[1] Rajalalitha P, Vali S. Molecular pathogenesis of oral submucous fibrosis–a collagen metabolic disorder. J Oral Pathol Med. 2005; 34(6): 321-8. doi.org/10.1111/j.1600-0714.2005.00325.x

[2] Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: review on aetiology and pathogenesis. Oral Oncol. 2006; 42(6): 561-8. doi.org/10.1016/j.oraloncology.2005.08.005.

[3] Chiu CJ, Chang ML, Chiang CP, Hahn LJ, Hsieh LL, Chen CJ. Interaction of collagen-related genes and susceptibility to betel quid-induced oral submucous fibrosis. Cancer Epidemiology Biomarkers & Prevention. 2002; 11(7): 646-53. doi: pubmed.ncbi.nlm.nih.gov/12101112/

[4] Bhuyan, R. ., Bhuyan, S. K., Panda, N. R. ., & Mohanty, J. (2022). Age and gender demographic and statistical analysis in oral squamous cell carcinoma in Eastern India. J Assoc Med Sc. 2023; 56(1): 35-9. doi: 10.12982/JAMS.2023.005.

[5] Modi MA, Dave VR, Prajapati VG, Mehta KA. A clinical profile of oral submucous fibrosis. NJIRM 2012; 3(3): 152-5.

[6] More CB, Gupta S, Joshi J, Varma SN. Classification system for oral submucous fibrosis. JIAOMR. 2012; 24(1): 24.

[7] Gupta MK, Mhaske S, Ragavendra R. Oral submucous fibrosis: current concepts in etiopathogenesis. Indian Dermatol Online J. 2014; 5(3): 260-5. doi.org/10.4103/2229-5178.137772.

[8] Kanthem RK, Guttikonda VR. Serum lipid profile in oral submucous fibrosis: A clinico pathological study. Journal of Oral and Maxillofacial Pathology: JOMFP. 2015 May; 19(2):139. [9]. Pandya S, Chaudhary AK, Singh M, Singh M, Mehrotra R. Correlation of histopathological diagnosis with habits and clinical findings in oral submucous fibrosis. Head Neck Oncol. 2009; 1: 10. doi.org/10.1186/1758-3284-1-10.

[9] Pandya S, Chaudhary AK, Singh M, Singh M, Mehrotra R. Correlation of histopathological diagnosis with habits and clinical findings in oral submucous fibrosis. Head Neck Oncol. 2009; 1:1-10. doi.org/10.1186/1758-3284-1-10.

[10] Sudarshan R, Annigeri RG. Pathogenesis of oral submucous fibrosis: The past and current concepts. J Oral Maxillofac Pathol. 2012 Apr 1; 3(2): 27-37. doi.org/10.1186/1758-3284-1-10.

[11] Chandran V, Anitha M, Avinash SS, Rao GM, Shetty BV, Sudha K. Protein oxidation: A potential cause of hypoalbuminemia in oral cancer. Biomed Res. 2012; 23(2): 227-30.

[12] Abhishek SN, Mubeen K, Vijayalakshmi KR, Suman B, Gayitri HC, Anitha M. Serum total protein, albumin and advanced oxidation protein products (AOPP)-implications in oral squamous cell carcinoma. Malays. J. Pathol. 2012; 34(1): 47-52.

[13] Singh P, Gharote H, Nair P, Hegde K, Saawarn N, Guruprasad R. Evaluation of cachexia in oral submucous fibrosis. JIAOMR. 2012; 24(2): 130-2. doi: 10.5005/jp-journals-10011-1277.

[14] Poli G, Leonarduzzi G, Biasi F, Chiarpotto E. Oxidative stress and cell signaling. Curr. Med. Chem. 2004; 11(9): 1163-82. doi.org/10.2174/0929867043365323.

[15] Patidar KA, Parwani RN, Wanjari SP. Correlation of salivary and serum IgG, IgA levels with total protein in oral submucous fibrosis. J Oral Sci. 2011; 53(1): 97-102. doi.org/10.2334/josnusd.53.97.

[16] Westra WH, Lewis JS. Update from the 4th edition of the World Health Organization classification of head and neck tumours: oropharynx. Head Neck Pathol. 2017; 11: 41-7. doi.org/10.1007/s12105-017-0793-2 PMID: 28247229.

[17] Dawood RM, Hasan HR. Assessment of salivary and serum proteins in patients with oral tumors. Baghdad Sci J. 2013; 10(03): 934-44. doi.org/10.21123/bsj.2013.10.3.934-944.

[18] Patel PS, Shah MH, Jha FP, Raval GN, Rawal RM, Patel MM, Patel JB, Patel DD. Alterations in plasma lipid profile patterns in head and neck cancer and oral precancerous conditions. Indian J Cancer. 2004; 41(1): 25-31.

[19] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer. 2015; 136(5): E359-86. doi.org/10.1002/ijc.29210 PMID: 25220842.

[20] Allampallam K, Dutt D, Nair C, Shetty V, Mundle S, Lisak L, Andrews C, Ahmed B, Mazzone L, Zorat F, Borok R. The clinical and biologic significance of abnormal lipid profiles in patients with myelodysplastic syndromes. J Cancer Stem Cell Res. 2000; 9(2): 247-55. doi.org/10.1089/152581600319469.

[21] Ernani V, Saba NF. Oral cavity cancer: risk factors, pathology, and management. Oncology. 2015; 89(4): 187-95. doi.org/10.1159/000398801 PMID: 26088938.

[22] Shih YH, Wang TH, Shieh TM, Tseng YH. Oral submucous fibrosis: a review on etiopathogenesis, diagnosis, and therapy. Int J Mol Sci. 2019; 20(12): 2940. doi: 10.3390/ijms20122940. PMID: 31208114; PMCID: PMC6627879.

[23] Chang YC, Tsai CH, Lai YL, Yu CC, Chi WY, Li JJ, Chang WW. Arecoline-induced myofibroblast transdifferentiation from human buccal mucosal fibroblasts is mediated by ZEB 1. J Cell Mol Med. 2014; 18(4): 698-708. PMID: 24400868, PMCID: PMC4000120 doi: 10.1111/jcmm.12219.

[24] Dubal M, Nayak A, Suragimath A, Sande A, Kandagal S. Analysis of smoking habits in patients with varying grades of smoker's palate in South Western region of Maharashtra. J Oral Res Rev. 2015; 7(1): 12. doi: 10.4103/2249-4987.160171.

[25] Xu H, Lyu FY, Song JY, Xu YM, Jiang EH, Shang ZJ, Chen LL, Xu Z. Research achievements of oral submucous fibrosis: progress and prospect. Biomed Res Int. 2021; Article ID 6631856, 10 pages. doi.org/10.1155/2021/6631856.

[26] Passi D, Bhanot P, Kacker D, Chahal D, Atri M, Panwar Y. Oral submucous fibrosis: Newer proposed classification with critical updates in pathogenesis and management strategies. J Maxillofac Surg. 2017; 8(2): 89-94. doi: 10.4103/njms.NJMS_32_17.