Original Article

Lipid profile in oral potentially malignant disorders and oral squamous cell carcinoma – A prognostic view

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Abstract

Introduction: Lipids play an important role in the maintenance of cell integrity. Various tobacco-associated products are known to induce the generation of free radicals and reactive oxygen species, responsible for the high rate of oxidation/peroxidation of polyunsaturated fatty acids. These further release peroxide radicals, causing increased utilization of lipids leading to hypolipidemia.

Aim: The aim of this study was to evaluate and compare the lipid profile pattern of patients with oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC) with healthy controls.

Material and Methods: The study included 90 subjects with 30 OPMDs, 30 OSCC and 30 healthy controls. Fasting blood samples were collected from subjects and were analysed for serum lipids, including the following: i) Total cholesterol (TC) ii) High-density lipoproteins (HDL) iii) Low-density lipoproteins (LDL) iv) Very low-density lipoproteins (VLDL) v) Triglycerides (TG) vi) CHO/HDL ratio by using semi auto analyser.

Statistical Analysis Used: The statistical tests used were the independent t-test, ANOVA test. A *P* value of <0.05 and <0.01 was considered statistically significant.

Results: A statistically significant decrease in serum TC, LDL and CHO/HDL ratio was observed among OPMD and OSCC groups than controls, whereas a significant decrease in serum VLDL and TG (p value <0.01) in poorly differentiated OSCC was seen.

Conclusion: The study shows an association between lipid variations and OPMD and OSCC. Low levels of lipids could be due to the rapidly dividing cells in premalignancies and malignancies utilizing them for new membrane biogenesis. Thus, lower lipid status may be a useful indicator for initial changes happening in neoplastic cells.

Keywords: Hypocholesteraemia, lipid profile, oral potentially malignant disorders, oral squamous cell carcinoma

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INTRODUCTION

Oral cancer is one of the most common forms of cancer around the world, with about 90 to 95% being oral squamous cell carcinoma (OSCC).[1] OSCC was also considered to be preceded by various oral potentially malignant disorders (OPMDs) with 2-12% of them

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transforming into cancers.[2] The survival rate of OSCC can be improved by early detection and treatment. The early detection of OPMDs prevents their progression to an invasive carcinoma which leads to increased quality of life among the patients. In recent years, prominence has been placed on detecting biomarkers from body fluids for predicting prognosis, and monitoring disease progression. One such biomarker can be '*Lipid profile*'.[3]

Lipids are present as membrane components of the cell and are essential for various biological functions, including cell division, growth of normal and malignant tissues. The newly proliferating tumour cells would require many basic components well above the normal limits, for the maintenance of structural and functional integrity of all biological membranes. The increased requirement of lipids to fulfil the need of these proliferating cells is expected to diminish the existing lipid stores (Hypocholesteremia).[4]

Various tobacco-induced products are known to induce the generation of free radicals and reactive oxygen species, which are responsible for the high rate of oxidation/peroxidation of polyunsaturated fatty acids (PUFA). This peroxidation further releases peroxide radicals causing increased utilization of lipids which is accomplished either from circulation or by synthesis through metabolism or degradation of major lipoproteins like very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL) causing hypolipidemia.[5-7] Based on the above facts, the present study aims at evaluating and comparing total cholesterol (TC), HDL, LDL, VLDL, triglycerides (TG), cholesterol (CHO)/HDL values in OPMDs, OSCC with respective controls using semi autoanalyzer. This study is the first of its kind to compare and evaluate lipid profile with grading and staging of OSCC and also with respect to different OPMDs like Oral submucous fibrosis (OSMF), leukoplakia and Oral lichen planus (OLP).

MATERIALS AND METHODS

The following study was conducted on 90 subjects after obtaining institutional ethical clearance (Drs. S&NRSIDS/IEC/19/2015). These subjects were divided into three main groups, and the first two groups were further divided into subgroups.

OPMDs group – people with oral potentially malignant disorders (N- 30), among which 10 each with oral submucous fibrosis, oral lichen planus and leukoplakia.

OSCC group – people with oral squamous cell carcinoma (N- 30) with different grades and clinical stages (TNM staging). Grading was done based on Broder's system. Out of 30, Well differentiated OSCC (WDOSCC-19), Moderately differentiated OSCC (MDOSCC-7) and Poorly differentiated OSCC (PDOSCC-4) were included. Also, among the same 30 patients, four were TNM stage 1, seven were TNM stage 2 and six each in TNM stages 3 and 4.

Control group – healthy individuals – 30 participants.

Inclusion criteria: Patients who were clinically and histopathologically diagnosed with oral potentially malignant disorders, histopathologically diagnosed oral squamous cell carcinoma patients and healthy patients without any oral lesions were included.

Exclusion criteria: Individuals suffering from any diseases that can alter lipid profile like Diabetes mellitus, uremia, nephritic syndrome, hypothyroidism, hyperthyroidism, acromegaly, and individuals on lipid-lowering drugs were excluded.

Sample collection: Five millilitre of fasting blood (12 hr) was collected under aseptic conditions, and TC, HDL, LDL, VLDL, TG and CHO/HDL ratios were analysed by using reagents such as cholesterol reagent, HDL reagent and triglycerides reagent in a semi autoanalyzer. VLDL was measured by using the formula – TRIGLYCERIDES/5, LDL was measured by using the formula LDL = TC – VLDL – HDL and CHO/HDL was analysed by dividing the total cholesterol value by HDL value. The obtained values were analysed statistically using SPSS software (version 2.0).

RESULTS

Descriptive analysis of OPMDs and OSCC groups are enumerated in Table 1.

Comparison of Serum Lipid Profiles in OPMD, OSCC and Control groups:

One-way ANOVA test was done for the comparison, which revealed that serum TC, HDL, LDL, and CHO/HDL ratio levels were decreased in OPMD, and OSCC groups compared to controls with TC, LDL and CHO/HDL ratio levels being statistically highly significant (p-value < 0.01, <0.01, <0.05 respectively). The serum VLDL and TG levels were increased among OSCC and OPMD groups compared to controls [Table 2].

Comparison of Serum Lipid Profiles between subgroups of OPMDs and Control group:

Table 1: Descriptive analysis of OPMDs and OSCC groups

	Age						Gender	
	21-30	31-40	41-50	51-60	61-70	71-80	Females	Males
OSCC								
Frequency	1	7	7	5	9	1	6	24
Percent	3.3	23.3	23.3	16.7	30	3.3	20	80
OPMD								
Frequency	9	3	7	4	7	0	9	21
Percent	30	10	23.3	13.3	23.3	0	30	70

Table 2: Comparison of serum lipid profile between OPMD, OSCC and control groups

Serum	Group	Mean	SD	*P*
TC	OPMD	171.50	29.68	
	OSCC	179.77	33.02	<0.01
	Control	198.07	32.08	
HDL	OPMD	47.33	8.60	
	OSCC	47.43	12.46	0.93
	Control	48.40	15.20	
LDL	OPMD	91.43	22.24	
	OSCC	98.33	34.88	<0.01
	Control	119.40	38.60	
VLDL	OPMD	33.07	12.53	
	OSCC	34.00	9.66	0.37
	Control	30.27	9.33	
TG	OPMD	165.53	62.77	
	OSCC	170.83	48.68	0.39
	Control	152.40	46.84	
CHO/HDL	OPMD	3.60	0.79	
	OSCC	4.02	1.35	<0.05
	Control	4.46	1.45	

In the OSMF group, decreased serum TC, HDL, LDL and CHO/HDL ratio was seen compared to controls, with TC, and LDL values being statistically highly significant (p-value < 0.01). However, the serum VLDL, and TG values were elevated in the OSMF group compared to controls.

The leukoplakia group showed decreased serum TC, LDL, and CHO/HDL ratio and elevated HDL, VLDL and TG values compared to controls, but the results were not statistically significant.

The lichen planus group revealed decreased serum TC, LDL and CHO/HDL ratio, with TC & LDL being statistically significant (p-value < 0.01, <0.05 respectively). Increased serum TG levels were observed compared to controls, and serum VLDL, and HDL values showed variable results among the two groups [Table 3].

Comparison of Serum Lipid Profiles among grades and stages of OSCC:

There was a gradual decrease of serum VLDL and TG values in poorly differentiated OSCC compared to well and moderately differentiated OSCC and were statistically highly significant (p-value <0.01). But the TC, HDL, LDL and CHO/HDL ratios showed variable alterations among the grades [Table 4]. A gradual decrease in serum TC values from stage I to stage IV was seen but not statistically significant [Table 5].

DISCUSSION

Lipids are a very heterogenous group of biomolecules that are generally insoluble in water but which readily dissolve in non-polar solvents, such as ether and chloroform.[8] They are a diverse class of biomolecules that are known to play key roles in cellular energy storage, structure and signalling. Dietary lipids are mostly in the form of TG, cholesterol and phospholipids.[9]

In recent years, researchers have stated the possible role of dietary and endogenous lipids in the aetiology and prognosis of cancer and precancer. Cholesterol, which is a known factor in the aetiology of coronary heart disease, has recently become the focus of attention on the possible role in the aetiology of cancer and precancer.[4]

Oral cancer is the most frequent cause of morbidity and mortality, which is usually preceded by oral potentially malignant disorders. Around 4-6% of leukoplakia, 4-13% of OSMF, 0.1-2.2% of OLP undergo malignant transformation. The treatment outcome and prognosis are better in patients with potentially malignant and malignant disorders if they are detected early.[2] Thus, the development of newer diagnostic and predictive approaches that are safe, economical and amenable to repeated sampling is imperative.[8,10]

In the present study, the majority of individuals in the OPMD group are between 21 and 30 years. This finding is in accordance with Antony George *et al*.[11] and they stated that 1-5% of OPMD affects the younger age group because of their early exposure to tobacco. In the OSCC group, elder ones are the most commonly involved (61-70). Similar observations were made by Giacomo D Corso *et al*.[12] & Alejandra Fernández[13] said that the median age of diagnosis for oral cancer was 64.5 years.

Table 3: Comparison of serum lipid profiles between subgroups of OPMD and control groups

	TC[†]	HDL[†]	LDL[†]	VLDL[†]	TG[†]	CHO/HDL[†]
OSMF	158.3±23.3*	42.8±7.96	81.3±19.0*	34.2±11.5	172.1±57.6	3.72±0.7
LEUKOPLAKIA	185±37.4	50.3±6.2	102.5±26.4	32.2±12.8	164.6±64.1	3.53±0.9
OLP	171.2±22.3*	48.9±10.0	90.5±16.7*	32.2±14.2	159.9±71.9	3.56±0.8
CONTROLS	198±32.0	48.4±15.2	119.4±38.6	30.27±9.3	152.4±46.8	4.46±1.4

[†] - Mean ±SD, * - statistically significant (<0.05)

Table 4: Comparison of serum lipid profile within the grades of OSCC

Serum	Grade	Mean	SD	*P*
TC	WDOSCC	177.58	32.46	
	MDOSCC	183	38.67	0.89
	PDOSCC	184.5	33.76	
HDL	WDOSCC	47.58	12.83	
	MDOSCC	47.43	15.74	0.99
	PDOSCC	46.75	3.95	
LDL	WDOSCC	93.16	37.9	
	MDOSCC	100.71	26.62	0.42
	PDOSCC	118.75	31.43	
VLDL	WDOSCC	36.84	7.21	
	MDOSCC	34.86	10.68	<0.01
	PDOSCC	19	3.16	
TG	WDOSCC	185.16	35.87	
	MDOSCC	176	53.04	<0.01
	PDOSCC	93.75	16.7	
CHO/HDL	WDOSCC	4.05	1.58	
	MDOSCC	4.01	1.06	0.98
	PDOSCC	3.9	0.63	

In both OSCC and OPMD groups, males outnumbered females. Same trend was reported by Antony George *et al*.,[11] Giacomo D corso *et al*.,[12] Alejandra Fernández[13] and V K Poorey *et al*.[14] stated that cancer was more common among men due to the increased incidence of tobacco addiction in them. In many countries, for example, India, there is a greater restriction on women's behaviour contributed to widespread social pressure against women's smoking.[15]

Comparison of Serum Lipid Profile between OPMDs, OSCC and control groups:

There was a statistically significant decrease in TC, LDL and CHO/HDL ratios in OPMDs and OSCC groups compared to controls [Table 2]. In our study, the possible mechanism of decrease in lipids (hypocholesteraemia) was depicted as follows [Flow Chart 1].

As various carcinogens induce the generation of free radicals and ROS, which were responsible for peroxidation of PUFA, cause oxidative damage to DNA and alter cell membrane constituents. This leads to increased cell proliferation/carcinogenesis. Increased demand for lipids for new membrane synthesis by proliferating cells or increased LDL receptor activity in these cells, or decreased food intake in affected individuals might lead to hypocholesteraemia. similar observations were reported by Garg *et al*.,[5] Gaddikeri K *et al*.[16]

It was also widely demonstrated that oral cancer interferes with food intake as well as lipid ingestion and absorption. Therefore, it can be expected that subjects with oral cancer have low levels of lipids.[17] The dietary saturated fat and cholesterol, vegetarianism can also be accounted for variations in lipid profile.

Comparison of Serum Lipid Profile between OSMF and Control group:

The study revealed a statistically significant decrease in TC, and LDL in the OSMF group than in controls [Table 3]. Areca nut being main aetiological agent causing OSMF, the major alkaloid arecoline undergoes nitrosation giving rise to N-nitrosamine, which might have a cytotoxic effect on the cells inducing the production of free radicals and ROS. Thus, affecting essential constituents of the cell membrane and might be involved in tumorigenesis resulting in greater utilization of lipids. Our findings are in total agreement with Altaf H Chalkoo *et al*.,[18] Gupta N *et al*.,[19] Mayeesh Radhakrishna *et al*.,[20] Ajai K *et al*.,[21] Goel P *et al*.[22]

Comparison of Serum Lipid Profile between Leukoplakia and Control group:

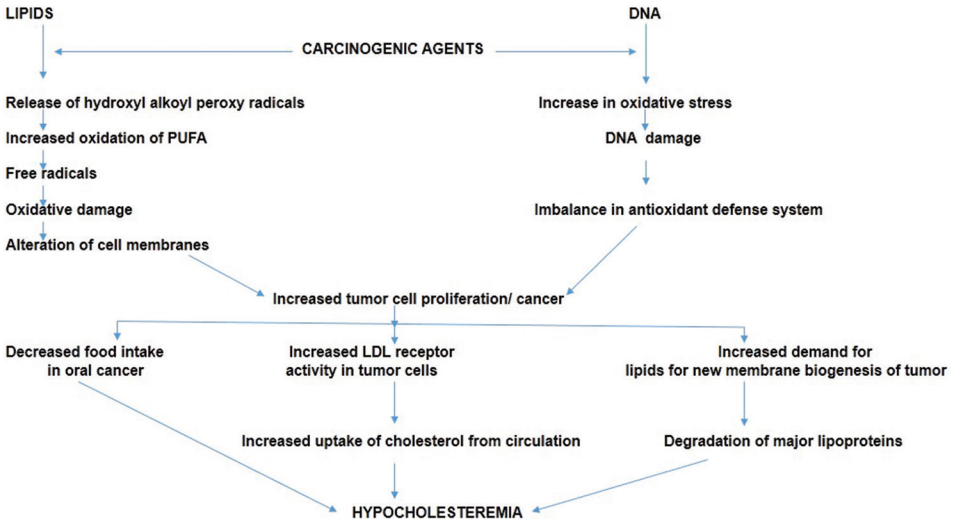
The serum TC, LDL and CHO/HDL ratio showed a slight decrease among the leukoplakia group compared with controls, and these findings coincide with BS Ganavi *et al*.,[23] Gupta S *et al*.[24] & Baduni *et al*.[25] [Table 3]. The major inducing factor for leukoplakia is tobacco, and the various carcinogens in it can stimulate the production of free radicals as well as reactive oxygen species, which cause an increased rate of oxidation/peroxidation of PUFA. This peroxidation causes the release of peroxide radicals which leads to increased consumption of lipids.

Comparison of Serum Lipid Profile between OLP and Control group:

We demonstrated that TC, LDL and CHO/HDL ratios were decreased in the OLP group compared with controls, with TC, and LDL being statistically significant [Table 3]. The LDL values correlate with the study done by Goel

Table 5: Comparison of serum lipid profile within the different stages of OSCC

	TC	HDL	LDL	VLDL	TG	CHO/HDL
Stage I	188.50±30.23	49.50±14.29	94.75±43.53	44.25±7.80	222.00±37.95	4.10±1.63
Stage II	186.57±37.09	57.14±15.90	92.57±35.01	36.86±10.3	184.71±53.69	3.53±1.65
Stage III	175.67±34.34	43.67±10.33	99.67±36.54	32.33±6.89	163.00±35.45	4.20±1.35
Stage IV	174.50±37.58	45.17±10.52	95.83±39.86	33.50±6.98	168.17±33.15	4.12±1.53
P	0.88	0.27	0.99	0.16	0.17	0.85



Flow Chart 1: The possible mechanism of decrease in lipids (hypocholesteraemia) in oral cancer and oral potentially malignant disorders

et al.[22] OLP represents a T cell-mediated inflammatory disorder. Inflammation produces lipid metabolism disturbances, such as an increase in TGs and a decrease in cholesterol & (LDL-C), which was in support with studies done by Lopez Jornet *et al*.,[26] Goel *et al*.,[22] Falguni H Panchal *et al*.,[27] Arias-Santiago *et al*.[28]

Comparison of Serum Lipid Profile between grades and stages of OSCC:

A comparison of different histological grades of the OSCC group revealed a statistically significant decrease in TG and VLDL, with poorly differentiated OSCC showing least values [Table 4]. Similar findings were demonstrated by S Acharya *et al*.,[9] Chawda *et al*.[29] The decrease in TG and VLDL might be due to the result of differential utilization of lipids by different grades of the lesion.

When clinical stages of OSCC were taken into consideration, no significant correlation of serum TC, HDL, LDL, VLDL, TG and CHO/HDL ratio was found [Table 5], which were in accordance with S Acharya *et al*.[9] & Li *et al*.[30]

Comparison of Serum Lipid Profile between OPMDs and OSCC groups:

Our study revealed that serum TC, LDL and TG levels were slightly decreased in OPMDs group but not statistically significant [Table 2]. These findings correlate with Patel PS *et al*.[6] and in contrast to Lohe V K *et al*.,[17] Rajul Mehta *et al*.[31] As the potentially malignant disorders have a higher rate of malignant transformation, the alteration of lipids might add to the evidence of their neoplastic transformation. Among OPMDs, the serum lipid profile was considerably low in OSMF compared to leukoplakia and OLP, and this can be attributed to the highest malignant transformation rate of OSMF (7-13%) compared to the other two.[32] The present study has some limitations with respect to sample size, where the efficiency of these markers can be estimated using multi-institutional trials with larger sample sizes and its correlation with various treatment outcomes.

CONCLUSION

A prominent association between lipid profile and OPMD and OSCC was observed with a decrease in lipid levels as the grade increases in OSCC. This can be attributed to the exhaustion of lipid levels for cell membrane synthesis by the growing tumour cells. Thus, lipid profile might help in assessing the course and prognosis of the disease with its advantages like simplicity, universal liability and patient compatibility with better outcomes in the patients.

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Conflicts of interest

There are no conflicts of interest.

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