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Original Research Article

Correlation of plasma lipid levels and histopathological grading in patients with oral squamous cell carcinoma and its pre-cancerous lesions

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ABSTRACT

Background: Lower levels of lipid in proliferating tissues and in blood compartments may occur due to ongoing process of oncogenesis. The evidence regarding hypolipidemia as a predisposing factor for malignancy is scarce. Therefore, this study was undertaken to study alteration of plasma lipid levels in patients diagnosed with oral squamous cell carcinoma (OSCC) and its oral pre-cancerous (OPC) lesions and also to compare the plasma lipid profile in different grades of OSCC.
Methods: A single centre prospective cross sectional study was carried out among 150 consecutive patients of OSCC and OPC lesions. The diagnosis of all lesions was confirmed histopathologically and grading was also done for each lesion based on degree of differentiation and keratinization of tumour cells. Serum total cholesterol, HDL, TG, LDL was estimated by using semi-automated chemical analyzer. The lipid levels were compared by using unpaired t-test between two strata whereas one way analysis of variance (ANOVA) with Tukey's post-hoc tests was used among more than two strata.
Results: Total cholesterol, TG, HDL, and LDL were significantly reduced in OSCC and OPC groups when compared with the reference values. Serum TC, LDL and HDL levels were found to be decreased with the loss of differentiation in histological grading but with no statistical significance.
Conclusions: It can be inferred that there is an inverse relationship between the serum lipid profile values of TC, HDLC, TG, LDL and OSCC as well as OPC patients. The lower serum lipid status may be considered a useful indicator for initial changes occurring in neoplastic cells.

Keywords: Oral squamous cell carcinoma, Histopathological grading, Oral sub-mucosal

INTRODUCTION

Oral cancer (OC) is often a matter of health concern all around the world as it is one of the most common cancers and is tenth most common cause of mortality.[1] There are several types of OC, but around 90% are squamous cell carcinoma.[2] Oral squamous cell carcinoma (OSCC) is often preceded by specific oral pre-cancerous lesions (OPC); the common among them are the oral leukoplakias and oral sub-mucous fibrosis (OSMF). These lesions display the metabolic and histological activity similar to cancerous lesions and have potential for malignant transformation. Around 0.3-25% of leukoplakias and 7-12% of oral sub-mucosal fibrosis will undergo malignant transformation.[3,4]

The biological activity of oral OSCC is classified as highly, moderately, poorly differentiated and anaplastic

according to borders histopathological grading.[5] A diversity in degree of differentiation can be observed at multiple locations in oral cavity at variable time span in a patient. This has led to inter-observer variation among different pathologists on the basis of dysplastic features leading to variable treatment plan for individual patient.

Well-known risk factors for OSCC and pre-cancerous lesions are chewing and sniffing of tobacco, areca nut and alcohol consumption in various forms, which results in increased free radicals formation. Free radicals will further cause lipid peroxidation, which in turn affects various cellular vital activities including growth, differentiation and gene expression.[6,7] Lipids are major cell membrane components which are important for various biological functions in body including cell growth and division of both normal and malignant cells.[8] Lipids primarily in the form of triglycerides and cholesterol, are transported in body fluids with the help of various lipoproteins (Chylomicrons, very low density lipoproteins-VLDL, low density lipoproteins-LDL and high density lipoproteins-HDL). Chylomicrons and VLDL are involved in transportation of triglycerides whereas LDL and HDL are involved in transport of cholesterol. Triglycerides, cholesterol, LDL–cholesterol and HDL–cholesterol primarily constitute plasma lipid profile as chylomicrons and VLDL are rapidly catabolized in the body.[9]

In some malignant diseases, blood lipid levels undergo early and significant changes. Lowered levels of blood cholesterol in the proliferating tissues and in blood compartments may be due to the ongoing process of oncogenesis. The question arises whether hypolipidemia is considered to be a predisposing factor or a consequence of malignancy. However, earlier studies have shown that hypolipidemia may result primarily due to the direct lipid-lowering effect of tumor cells and secondarily to either malfunction of the lipid metabolism or antioxidant vitamins. These studies have shown that lower blood lipids have been associated with various cancers.[10-13]

Considering these curiosities, we aimed to study the alteration of plasma lipid levels in patients diagnosed with OSCC and its OPC and also to compare the plasma lipid profile in different grades of OSCC.

METHODS

A single centreprospective cross sectional study was carried out among 150 consecutive patients of OSCC and OPC lesions attending OPD and IPD of Department of ENT and Head, Neck Surgery, King Georges Medical University Hospital, Lucknow, UP, India for the period of 1.5 year (December 2014 to July 2016). Informed written consent was taken from each patient. The ethical committee of KGMU has approved the current study. All patients with OSCC and OPC lesions were diagnosed on the basis of histopathological examination and further staged according to TNM staging of oral tumors (AJCC Cancer Staging Manual).[14] Those patients willing to undergo examination and biopsy, were included in the study. These patients were categorized under five groups according to the degree of differentiation on the basis of histopathology: Group 1: OPC Group, patients who have histopathologically confirmed diagnosis of precancerous lesion (leukoplakia, dysplasia, etc); Group 2: Highly Differentiated OSCC; Group 3: Moderately differentiated OSCC; Group 4: Poorly differentiated OSCC; Group 5: Anaplastic or pleomorphic type differentiated OSCC. Those patients who were non-compliant, had prior treatment history with surgery, radiation or chemotherapy, having co-morbid illnesses such as diabetes, obesity, hypertension, anemia, jaundice, liver or kidney disorders or any other systemic diseases as well as malignancies detected elsewhere in the body and currently taking drugs that alter the lipid levels, were excluded from the study.

A comprehensive history was carefully obtained with special reference to their tobacco habits, its nature, duration and frequency of use and also to rule out any exclusion criteria. Detailed physical examination and clinical staging of OSCC and OPC lesions was done. All patients underwent routine blood investigations along with plasma lipid profile. Radiological (chest x-ray, CT/MRI head and neck and USG abdomen) as well as histopathological (incisional biopsy of mucosal lesion) investigations were performed in every patient depending on the site of involvement. Fibreoptic nasal and laryngeal endoscopic examination and FNAC of cervical lymph nodes were performed wherever indicated.

Incisional biopsy was taken from suspected lesion in oral cavity, after getting an informed consent signed by the patient, biopsy was performed in all cases from the desired site(including normal tissue) with patient in supine position after sterile preparation of the biopsy site and infiltration with local anaesthetic agent (2% lignocaine). The biopsy tissue was then placed in a small vial containing 10% neutral buffered formalin for 12-24 hours. The tissue was then embedded with paraffin wax, processed and stained. Section were stained with hematoxylin and eosin stain for morphological assessment as per the standard protocols. The hematoxylin used was Harris hematoxylin and eosin used was eosin Y. Border's system was used for histopathological grading based on degree of differentiation and keratinization of tumour cells.[5]

Lipid profile estimation: Fasting blood samples were collected from the subjects, into EDTA containing vacuettes. Serum total cholesterol, HDL, TG, LDL was estimated by using semi-automated chemical analyzer using colorimetric method (Selectra Pro M, ELITech Group-Biomedical Systems Division, USA) with the help of reagent (Q line, POCT Services Private Limited, New Delhi, India). Lipid profile with following range were used. (Total cholesterol: - borderline high -200-239

mg/dl; high- ≥240 mg/dl; TG:- borderline high- 150-199 mg/dl; high- 200-499 mg/dl; HDL:- low <40 mg/dl; high >60 mg/dl; LDL:- high >150 mg/dl)

Statistical analysis

The results were analyzed in mean, standard deviation (SD) and percentages. The lipid levels were compared by using unpaired t-test between two strata. The one way analysis of variance (ANOVA) with Tukey's post-hoc tests was used to compare the lipid levels among more than two strata. The $p<0.05$ was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

RESULTS

Out of 180 patients, a total of 150 cases were included in the study. 30 cases were excluded from the study(Non-compliant-10, Prior treatment history with surgery, radiation or chemotherapy-12, Co-morbid illnesses such as diabetes, obesity, hypertension, anemia, jaundice, liver or kidney disorders or any other systemic diseases-11, Malignancies detected elsewhere in the body-2 and currently taking drugs that alter the lipid levels-6). Among 150 patients, 128 cases belong to OSCC and 22 to OPC group. The clinical and demographic profile of 150 patients has been described in Table 1. The mean age of 150 patients was 48.00±13.71 (22-86) years. Further, studying gender distribution in the study group, majority of the cases were found to be males 114 (76%) and only 36 (24%) were females. Most of the cases were consuming tobacco in one or other form with majority of cases were tobacco chewers 90 (60%) followed by smokers 56 (37.7%) and 40 (26.7%) cases were both chewers and smokers. Depending on the various sites of involvement in oral cavity, tongue was most commonly involved in 45(30%) cases, followed by buccal mucosa 36 (24%) and least involving floor of mouth in 6 (4%) cases.

Table 1: Distribution of patients according to clinical and demographic variables.

	Parameters	No. (N=150)	Percentage (%)
Age (in years)	<30	10	6.7
	31-40	39	26.0
	41-50	43	28.7
	51-60	29	19.3
	>60	29	19.3
	Mean±SD (Range)	48.00±13.71 (22-86)	
Gender	Male	114	76.0
	Female	36	24.0
Tobacco habit	Chewing	90	60.0
	Smoking	56	37.7
	Both	40	26.7
Family history of cancer in first degree relative	Present	13	8.7
	Absent	137	91.3
Site of involvement in oral cavity	Upper lip	12	8.0
	Lower lip	13	8.7
	Buccal mucosa	36	24.0
	Gums	16	10.7
	Hard palate	11	7.3
	Tongue	45	30.0
	Floor of mouth	6	4.0
	Retro molar trigone	11	7.3
Histological diagnosis	Leukoplakia with dysplasia	5	3.3
	Leukoplakia without dysplasia	17	11.3
	OSCC	128	85.3
Staging of cancer	Stage I	19	15.4
	Stage II	17	13.2
	Stage III	56	43.7
	Stage IV	36	28.1
Histopathological grading according to degree of differentiation	Pre-cancerous lesions	22	14.7
	Well differentiated	73	48.7
	Moderately differentiated	46	30.7
	Poorly differentiated	9	6.0

Table 2: Comparison of lipid levels with various clinical as well as demographic variables.

		Cholesterol	P value	TG	P value	HDL	P value	LDL	P value
Age in years	<30	150.03±27.92	0.40	75.93±48.61	0.86	38.27±13.89	0.81	92.40±37.0	0.48
	31-40	148.45±28.47		76.51±54.80		38.07±9.38		102.07±32.88	
	41-50	139.56±30.69		70.76±59.51		37.33±7.36		93.32±26.55	
	51-60	148.14±35.93		79.84±74.46		39.48±9.86		95.70±28.39	
	>60	136.25±36.66		87.87±69.74		39.72±9.51		89.19±29.66	
Gender	Male	147.53±32.56	0.007*	83.55±67.11	0.04*	39.41±9.63	0.02*	94.71±29.42	0.72
	Female	131.09±28.37		59.43±39.93		35.48±7.26		96.74±31.79	
Tobacco habit	Chewing	147.72±32.19	0.06	84.05±67.50	0.13	39.64±9.25	0.06	97.75±31.86	0.20
	Non chewing	137.39±31.69		68.12±52.83		36.70±9.03		91.37±26.54	
	Smoking	141.21±32.03	0.48	78.75±65.57	0.89	37.81±9.71	0.50	94.32±29.06	0.78
	Non smoking	145.01±32.53		77.33±61.01		38.85±8.99		95.72±30.55	
	Both	145.07±33.42	0.73	80.98±63.35	0.41	39.36±10.25	0.47	96.44±31.00	0.75
	None	143.05±32.01		76.69±62.45		38.14±8.88		94.74±29.64	
Site of involvement in oral cavity	Upper lip	147.89±40.20	0.006*	33.15[a]±17.09	0.001*	41.54±7.03	0.07	86.15±21.34	0.40
	Lower lip	125.20[a]±33.83		41.77[b]±31.87		37.51±9.02		97.84±26.90	
	Buccal mucosa	157.77[a]±27.54		119.82[a,b]±72.82		41.28±12.13		102.84±29.05	
	Gums	134.03±35.15		62.24±72.55		33.68±6.20		85.04±33.23	
	Hard palate	127.56±26.62		34.24±21.53		34.41±5.21		87.15±30.45	
	Tongue	144.08±28.10		86.42±53.93		37.94±8.80		96.68±33.21	
	Floor of mouth	122.72±25.78		38.66±11.19		36.28±2.73		84.42±25.88	
	Retromolar trigone	153.55±37.07		83.70±54.74		41.34±8.33		99.54±24.17	
Histological diagnosis	Leukoplakia with dysplasia	133.94±37.24	0.67	72.88±67.82	0.22	38.92±10.98	0.96	109.90±15.79	0.53
	Leukoplakia without dysplasia	148.14±31.41		103.43±52.04		38.94±7.64		94.72±25.03	
	OSCC	143.36±32.38		74.73±63.23		38.38±9.44		94.68±30.89	
Histopathological grading according to degree of differentiation	Pre-cancerous lesions	144.91±32.45	0.13	96.16±55.94	0.21	38.94±8.21	0.98	98.17±23.82	0.71
	Well differentiated	141.87±30.36		79.87±71.22		38.52±10.98		96.18±29.61	
	Moderately differentiated	149.71±34.93		71.50±51.87		38.35±7.40		94.19±33.89	
	Poorly differentiated	123.06±27.77		43.40±29.27		37.41±4.49		85.07±25.97	
Mouth opening	Restricted	138.43±33.97	0.01*	67.33±61.21	0.01*	37.91±8.29	0.36	92.35±29.14	0.14
	Not restricted	151.54±27.96		93.92±61.53		39.32±10.57		99.59±30.81	

Furthermore, there is significant family history of cancer in first degree relative of 13 (8.7%) cases. Majority of cases 128 (85.3%) were histologically proven as OSCC, followed by leukoplakia without dysplasia 17 (11.3%) and leukoplakia with dysplasia 5 (3.3%). Among 128 cases of oral cancer, 19 patients were in stage I (15.4%), 17 in stage II (13.28%), 56 in stage III (43.7%) and 36 in stage IV (28.1%). On histopathological examination majority of the patients were well differentiated carcinoma 73 (48.7%) followed by moderately differentiated carcinoma 46 (30.7%), pre-cancerous lesion in 22 (14.7%) and poorly differentiated carcinoma 9 (6%). None of the patients belong to anaplastic type.

The comparison of lipid levels with various clinical as well as demographic variables has been described in Table 2. It was observed that mean total cholesterol in all age groups was lower than the reference value for total cholesterol (200-239 mg/dl). Similarly total triglyceride (reference value 150-199 mg/dl), HDL cholesterol (reference value <40 mg/dl) and LDL (reference value <150 mg/dl) was also lower than their normal reference values in all age groups. There was no significant ($p>0.05$) difference in the lipid levels among the different age groups. Furthermore, it was seen that total cholesterol, triglyceride, HDL and LDL was lowered in both sexes in comparison to normal reference values. Cholesterol ($p=0.007$), TG ($p=0.04$) and HDL ($p=0.02$) found to be significantly lower among females than males. However, there was no significant ($p>0.05$) difference in LDL between male and female. There was no significant ($p>0.05$) difference in the lipid levels between tobacco users and non-users. Further comparing plasma lipid profile with different sites of involvement, the cholesterol ($p=0.006$) and TG ($p=0.001$) was found to be significantly different among different sites. The post-

hoc comparison tests showed that TG was significantly ($p<0.05$) different between upper lip and buccal mucosa. However, there was no significant ($p>0.05$) difference in cholesterol, HDL and LDL among the sites. Comparing the plasma lipid profile among cancer and precancerous lesions patients, ANOVA revealed no significant ($p>0.05$) difference in cholesterol, TG, HDL and LDL levels among the cancer and precancerous cases. Further comparing lipid levels with HPE. There was no significant ($p>0.05$) difference in cholesterol, TG, HDL and LDL among the various grades of HPE. There was significant ($p=0.01$) difference in cholesterol and TG (0.01) between restricted and not restricted mouth opening.

DISCUSSION

In the present study, alteration of lipid profile parameters of OSCC and OPC cases were evaluated and also compared as well as correlated among different grades of OSCC.

In the present study maximum number of patients of OSCC and OPC were found between 41 to 50 years of age. This was supported by another study that also observed that the carcinoma of aero-digestive tract was more prevalent in the age group of 41 to 60 years (65.6%).[15] The current study group comprised predominantly males. This was observed in other studies which stated that the OSCC have male predominance.[16-18] However, few studies have shown female predominance as well.[18,19] The result of present study showed that most of the cases are addicted to tobacco, 60% of patients are tobacco chewers, 37.7% tobacco smokers and 26.7% are both chewers and smokers. It is in concordance with a meta-analysis that revealed that Oral cavity cancer risk is 3 times higher in current smokers compared with never-smokers.[20] A pooled analysis showed oral cavity cancer risk in men is almost 3 times higher in those who have smoked the most cigarettes for the most years, compared with those who have smoked the least for the fewest years.[21] Oral cavity cancer risk in women is 4 times higher in the heaviest- and longest-smokers as compared to the lightest- and shortest-smokers.[21] Positive history of cancer in first degree relative also increases the risk of cancer. In present study 13 (8.7%) had positive family history of cancer. In present study, various sites are involved in this frequency, most common is tongue which was found in 45 (30%) cases, followed by buccal Mucosa 36 (24%) and least involving floor of mouth 6 (4%). Previous studies showed that, buccal mucosa is most common site of oral cancer in South East Asia, which constitute upto 40 percent of oral cancers arising at this site. This contrasts with North America and Western Europe where buccal carcinoma is less common and only accounts for 2-10% of oral carcinoma.[22,23] We are receiving patients with malignancy in advanced cancer stage III and IV at our apex centre. This could be because of poor socioeconomic status and lack of awareness. In present study, on histopathological examination, well differentiated grade (48.7%) came out to be most common type and there is no case of anaplastic or pleomorphic type which is in agreement with Akinyamoju et al who found that 31.3% of cases were well differentiated tumours, 50% were moderately differentiated while 18.7% were poorly differentiated.[24]

The results of the present study show that total cholesterol, TG, HDL, and LDL were significantly reduced in the OSCC and OPC groups when compared with the reference values which is in agreement with studies reported by Ashutosh et al and Garg et al.[25,26] Other studies have also reported decreased lipid levels in cancer patients but with variable lipid profile patterns as compared to control group.[27-38] Lohe et al and Patel et al found a significant decrease in TC, HDL, VLDL, and TG but not in LDL in patients with OSCC.[1,8] Acharya et al reported significant decrease in TC, HDL, LDL, and VLDL but not for TG in patients with OSCC.[3] Nydegger et al observed a decrease in α - lipoprotein and cholesterol levels and was possibly due to increased catabolism of α – lipoprotein and cholesterol, decreased synthesis of α–lipoprotein and cholesterol by liver as the synthesis is affected by tumor metabolites.[39] In neoplastic tissue, an increased level of low density lipoprotein activity in tumor cells may produce hypocholesteremia. Blood cholesterol is believed to undergo significant changes early on in the process of carcinogenesis. Schatzin et al and Chyou et al have observed an inverse relation between lower serum cholesterol level and head, neck cancer and as well as oesophageal cancers.[40,41] Sherubin et al observed a significant decrease of all lipid levels in patients with oral malignancy.[42] Alexopolus et al have found non-significant difference in serum triglyceride levels between controls and patients.[13] The results are strengthen by the present study which also shows lower levels of serum levels of total cholesterol, Triglycerides, HDL, VLDL, LDL in oral cancer and precancerous lesion patients. The present study also reported that on comparing lipid levels among gender group, cholesterol ($p=0.007$), TG ($p=0.04$) and HDL ($p=0.02$) found to be significantly lower among females than males. However, there was no significant ($p>0.05$) difference in LDL between male and female. Since oral squamous cell carcinoma is more often than not preceded by OPC lesions, an attempt was made to analyze the serum lipid profile in OPC lesions patients as well. In comparison to normal reference values of plasma lipid profile, the levels of Total Cholesterol, TC, HDL, and LDL were lower in the OPC group but the results were not significant statistically. However, other studies have found a significantly lower level of TC and HDL in patients with OPC lesions. Nayak et al and Mehrotra et al found significantly lower level of TC and HDL in pre-malignant oral sub-mucous fibrosis when compared with controls.[27,43] There is no significant difference between plasma lipid levels in oral cancer patients and patients with precancerous lesion in our study, findings contrary to those of Lohe et al which indicate overutilization of lipids during transformation from oral pre-cancer to

cancer.[1] All these aforementioned studies have clearly reported that cancer patients exhibit irregular serum lipid patterns as compared to healthy subjects supporting the implication of an aberrant lipid profile in OSCC and OPC patients. Dysregulated lipid metabolism is considered to be hallmark of cancer. Although, serum TC, LDL and HDL levels decreased with the loss of differentiation in histological grading, the findings were not significant statistically. Similar findings were observed in the study of Lohe et al who found no significant correlation between histological grading and serum lipid profile in OSCC and OPC lesions.[1] In our study we observed a reduction in the total cholesterol, TG, LDL and HDL in all forms of tobacco users with OPC and OSCC patients which is in agreement with Kumar et al observed significant decrease of serum total cholesterol and HDL in OPC subjects with tobacco consumption habits as compared with controls who have no habit of tobacco consumption.[44] However, other studies have reported different findings. A study by Phillips et al reported that the serum triglyceride, VLDL, LDL level increased whereas serum HDL levels decreased with the number of cigarettes smoked daily.[45] The hyper-cholesterolemic state in tobacco users as reported by various studies was raised total cholesterol, LDL cholesterol, VLDL-cholesterol and, triglycerides and lowered HDL levels in tobacco users as compared to controls.[46-50] It can be inferred that there is an inverse relationship between the serum lipid profile values of TC, HDLC, TG, LDL and OSCC as well as OPC patients. The lower serum lipid status may be considered a useful indicator for initial changes occurring in the neoplastic cells. The exact role of altered serum lipid levels in the development of OSCC and OPC lesions requires further study with larger number of samples from various centres. Studies related to molecular genetics are essential in near future in order to explain the basic mechanisms and implications of serum lipids in cancer progression.

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