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RESEARCH ARTICLE

ESTIMATION OF SERUM LIPID AND LIPOPROTEINS IN ORAL SQUAMOUS CELL CARCINOMA AND POTENTIALLY MALIGNANT DISORDERS

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ABSTRACT

Introduction: Changes in the lipid profile are said to be associated with oral cancer and potentially malignant disorders. Incidence of cancer has been reported to be more in patients with reduced cholesterol levels. Patients with oral cancer with reduced cholesterol are said to be having higher mortality. We carried out a hospital based case control prospective study to assess the relationship between lipid profile and oral squamous cell carcinoma and potentially malignant disorders (leukoplakia and OSMF).

Aim and objective: To evaluate alteration of serum lipid profile in oral squamous cell carcinoma and potentially malignant disorders (leukoplakia and OSMF).

Material and method: The study consisted of 50 patients each of oral squamous cell carcinoma and potentially malignant disorders (30 OSMF & 20 Leukoplakia) and 50 controls. Lipid profile included analysis of total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), very low density lipoprotein cholesterol (VLDL), triglycerides (TGL) and ratio of high and low density lipoprotein cholesterol. Lipid profiles were measured using the standard reagents.

Result and observation: We found TG, LDL & VLDL were more in males in all the 3 groups. TC and HDL was highest in the females, however it was found to be higher than males in all the three groups but were non significant. A significantly reduced serum level of HDL, VLDL, TGL, TC and LDL were also reduced in the disease groups. When we correlated histological grading and lipid profile, well differentiated OSCC had low TC, and HDL, moderately differentiated had increased TG, LDL, and VLDL. TGL were highest in patients who had mildly dysplastic leukoplakia and lowest TC, while, moderate dysplasia cases had highest TC and lowest Tg, LDL, VLDL, HDL. Also in OSMF, most cases showed early changes (65%) and 35% cases showed moderately advanced changes. TC, Tg, LDL, VLDL, HDL levels were lowest compared to moderately advanced stage.

Conclusion: The reduced levels of lipid profile in cases of OSCC could be due to the increased utilization of cholesterol by the cancer cells and in case of potentially malignant disorders this could be due to tobacco habits that reduced the lipid fractions. The reduced levels of lipids in leukoplakia and OSMF could be used to assess the malignant transformation that could help in early detection and prevent the progression to carcinoma.

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INTRODUCTION

Oral squamous cell carcinoma is the commonest type of malignancy in India accounting for 30-40% of all cancers. The cancer control programs are based on the concept that earlier the cancer is diagnosed; the better is the outcomes in terms of increased survival and reduced mortality. Oral cancer is usually preceded by the occurrence of premalignant lesions or conditions (Manoharan *et al*., 2005) Leukoplakia, a potentially malignant disorder (PMD), plays a vital role in pathogenesis of oral squamous cell carcinoma (OSCC) in the oral cavity. The risk of neoplastic transformation varies from 0.3 to 25%.

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Presence of dysplasia in leukoplakia increases incidence of malignancy over 30%. (Sleron *et al*., 2003) Oral submucous fibrosis (OSMF) shows a significant tendency to develop cancer. Hence, it is important to detect and control the PMD's. Proliferation, differentiation and apoptosis are fundamental aspects of tumor biology. Sustained precancer and cancer growth needs a positive balance between malignant cell proliferation and cell apoptosis (Cheng, 2004). In recent years, emphasis is made on molecular markers to detect cancer from body fluid, like saliva, urine etc, to predict prognosis, and monitor disease progression (Schatzkin, 1988). The idea of screening and following patients with malignancy by blood-based tests is interesting due to its ease, economic advantage, non-invasiveness, and possibility of repeated sampling (Kark *et al*., 1982). Variations in tissue blood cholesterol levels in diagnosing and treating various diseases has been studied by several workers. Researchers have reported association of plasma/serum lipids and lipoproteins with different cancers, but only few studies are reported on association with head and neck cancers (Schatzkin *et al*., 1988; Chyou *et al*., 1992) However, past studies were limited, in that; they evaluated lipid profile only in cancer patients, whereas the present study evaluated lipid profile not only in oral cancer patients but also in the PMD patients. Further, this study compares and correlates serum lipid profile with histological gradings in oral cancer and PMD.

MATERIALS AND METHODS

The study subjects comprised of three groups as follows:

- **Group A:** Healthy controls
- **Group B:** Subjects with potentially malignant disorder (PMD)
- **Group C:** Subjects with oral squamous cell carcinoma (OSCC)

Method of Examination and Confirmation of Clinical Diagnosis

Examination of the patients was carried with mouth mirror and probe under artificial light and clinical photographs were obtained. Routine blood investigation and blood pressure estimation were done for all subjects to rule out any systemic diseases.

Collection of venous blood

After a thorough medical history,12 hour Fasting Venous blood was drawn from forearm of 50 patients each of healthy inividuals(Group A) and 50 clinically and histopathologically diagnosed cases of Potentially Malignant Disorders (Group B), and 50 OSCC (Group C). Patients were informed about the procedure and written consent was taken. After the histopathological confirmation based on above mentioned features, fasting blood samples were collected from the subjects, into sterile plain vials. Samples were allowed to clot for 1 hour at 37^0C & then stored at 4^0 c till analysed. Serum total cholesterol (TC), high density lipoprotein (HDL) & low density lipoprotein (LDL) were estimated by colorimetric methods using cholesterol kit obtained from span diagnostic Ltd. Serum lipid profile was estimated using cholesterol kits obtained from span diagnostic Ltd. TC was estimated by mixing 0.01ml serum sample with 1ml of working reagent. TG was estimated by mixing 0.01ml serum sample with 1ml of triglyceride assay reagent. HDL was estimated by mixing 0.2ml serum sample with 0.2ml HDL precipitating reagent followed by 10 minute incubation at room temperature. Supernatant was formed by centrifugation at 2800 g for 10 minutes and was mixed with 1ml of cholesterol reagent. The above 3 Mixtures obtained were incubated at 37^{0c} C for 10 minutes & measured using a spectrophotometer at 505nm against blank using distilled water and were calculated as follows:

TG (mg/dl) = absorbance of test/ absorbance of standard × 200
TC (mg/dl) = absorbance of sample/absorbance of standard ×200
HDL (mg/dl) = absorbance of sample /absorbance of standard× concentration of standard
LDL = Total cholesterol- triglycerides/5- HDL
VLDL = triglyceride / 5

Statistical analysis

One way ANOVA was used for multiple group comparison followed by students "t" test for two group comparison. Pearson correlation coefficient was used to measure the relationship between variables. For all the tests a "P" of 0.05 or less was considered for statistical significance.

RESULTS

Comparison of serum lipid profile in all 4 study groups

TC was lowest in leukoplakia followed by OSCC, while it was highest in OSMF followed by control group. When controls were compared to PMD and OSCC group the differences were highly significant ($p<0.001$). LDL levels were more in following order OSCC, OSMF and leukoplakia and difference was significant ($p<0.002$). HDL level was lowest in OSCC followed by OSMF and leukoplakia with difference being significant ($p<0.001$). VLDL was lowest in OSCC followed by controls and leukoplakia while it was increased in OSMF with significant difference ($p<0.001$). TG was lowest in OSCC, leukoplakia and controls while it increased in OSMF and differences were significant ($p<0.001$). (Table 1)

Correlation of lipid profile between subgroups

Difference in TC between control group and OSMF and OSCC was statistically insignificant (P 0.98, 0.78). The difference between control group and leukoplakia and was significant ($P<0.001$). The difference between OSMF with leukoplakia highly significant ($P<0.001$). But the difference between OSMF with OSCC was insignificant (P 0.64). Difference in TG between OSMF with leukoplakia and OSCC was highly significant ($P<0.001$). But the difference between leukoplakia and OSCC was insignificant ($p>0.35$). Difference of HDL between OSMF with leukoplakia and OSCC was insignificant (P 0.99 and 0.87 respect.) also difference between leukoplakia and OSCC was insignificant (P 0.79). The difference between control group and precancers (OSMF and Leukoplakia) was insignificant (0.15 and 0.67) and OSCC was statistically highly significant ($P< 0.001$). The difference in LDL between OSMF with leukoplakia and OSCC was insignificant (P 0.90 and 0.64 respect.) also difference between leukoplakia and OSCC was insignificant (P 0.29).

Table 1. Lipid profile in all groups

		N	Mean	Std. Deviation	Statistics/ Mean Squares	df2 (welch)/ F (Anova)	p value
Age	Control	50	40.5	14.227	15.066	61.567	<0.001
	Osmf	30	32.5	10.741			
	Leukoplakia	20	44.15	11.878			
	Oral Squamous Cell Carcinoma	50	48.26	9.356			
	Total	150	41.97	12.981			
Triglyceride -100-150mg/dl	Control	50	95.04	12.6442	22.937	64.634	<0.001
	OSMF	30	121.6	25.4296			
	Leukoplakia	20	79.05	11.1849			
	Oral Squamous Cell Carcinoma	50	91.978	45.1818			
	Total	150	97.199	32.2572			
Total Cholesterol & lt; 250mg/dl	Control	50	154.04	16.9006	27.53	67.28	<0.001
	OSMF	30	156.367	19.8433			
	Leukoplakia	20	120.05	14.4312			
	Oral Squamous Cell Carcinoma	50	148.63	42.871			
	Total	150	148.17	30.5425			
HDL N-40-50 mg/dl	Control	50	41.62	2.962	68.383	55.177	<0.001
	OSMF	30	31.8	4.238			
	Leukoplakia	20	31.4	13.766			
	Oral Squamous Cell Carcinoma	50	32.88	4.392			
	Total	150	35.38	7.534			
LDL -N 100-130	Control	50	98.28	18.0329	2234.483	4.999	0.002
	OSMF	30	108.623	9.61			
	Leukoplakia	20	104.55	15.3296			
	Oral Squamous Cell Carcinoma	50	114.392	29.3425			
	Total	150	106.555	21.9775			
VLDL-4-40mg/dl	Control	50	18.5	1.8871	11.96	49.434	<0.001
	OSMF	30	24.393	5.1895			
	Leukoplakia	20	20.45	12.0152			
	Oral Squamous Cell Carcinoma	50	17.556	11.7444			
	Total	150	19.624	8.7586			

Table 2. Correlation of lipid profile in subgroups

Dependent Variable	(I) Group	(J) Group	P Value
Age	Control	OSMF	0.02
		Leukoplakia	0.646
		Oral Squamous Cell Carcinoma	0.007
	OSMF	Leukoplakia	0.004
		Oral Squamous Cell Carcinoma	<0.001
	Leukoplakia	OSMF	0.004
		Oral Squamous Cell Carcinoma	0.552
Triglyceride-100-150mg/dl	Control	OSMF	0.001
		Leukoplakia	0.181
		Oral Squamous Cell Carcinoma	0.955
	OSMF	Leukoplakia	<0.001
		Oral Squamous Cell Carcinoma	<0.001
	Leukoplakia	OSMF	<0.001
		Oral Squamous Cell Carcinoma	0.357
Total Cholesterol & Lt; 250mg/dl	Control	OSMF	0.985
		Leukoplakia	<0.001
		Oral Squamous Cell Carcinoma	0.78
	OSMF	Leukoplakia	<0.001
		Oral Squamous Cell Carcinoma	0.646
	Leukoplakia	OSMF	<0.001
		Oral Squamous Cell Carcinoma	0.001
HDL N-40-50 mg/dl	Control	OSMF	<0.001
		Leukoplakia	<0.001
		Oral Squamous Cell Carcinoma	<0.001
	OSMF	Leukoplakia	0.996
		Oral Squamous Cell Carcinoma	0.871
	Leukoplakia	OSMF	0.996
		Oral Squamous Cell Carcinoma	0.799
Ldl -N 100-130	Control	OSMF	0.152
		Leukoplakia	0.677
		Oral Squamous Cell Carcinoma	0.001
	OSMF	Leukoplakia	0.909
		Oral Squamous Cell Carcinoma	0.64
	Leukoplakia	OSMF	0.909
		Oral Squamous Cell Carcinoma	0.297
VLDL-4-40mg/dl	Control	OSMF	0.016
		Leukoplakia	0.82
		Oral Squamous Cell Carcinoma	0.944
	OSMF	Leukoplakia	0.374
		Oral Squamous Cell Carcinoma	0.003
	Leukoplakia	OSMF	0.374
		Oral Squamous Cell Carcinoma	0.569

The difference in VLDL between OSMF with leukoplakia was insignificant (P 0.37) and with OSCC was significant (P 0.003) also difference between leukoplakia and OSCC was insignificant (P 0.569). (Table 2)

Correlation between lipid profile and potentially malignant group

The precancer group that included OSMF and leukoplakia was divided into smoking and smokeless tobacco chewing habit group. The difference between lipid profile and smokeless tobacco was highly significant in OSMF group. (Table 3)

Correlation of lipid profile with gender

Control group had 50% females and 62% males. In PMD 100% males were in OSMF, 80% males and 20% females in leukoplakia. In OSCC group 30% females and 70% males were present. There was significantly higher number of males in each group, but difference between the lipid levels were insignificant (p>0.168). (Table 4, graph 1)

Correlation of Histopathological changes with lipid profile

Dysplastic changes in leukoplakia: In mild dysplasia, the total cholesterol is 117.5±7.1, triglyceride is 79.3±9.5, VLDL is 22.71±13.5 and are significant (P 0.001, 0.001 and 0.002). The HDL is 33.1±14.5 and LDL is105.5±15.8 and are non significant (P 0.822 and 0.31). In moderate dysplasia, total cholesterol, triglyceride, VLDL levels were 125.8±24.4, 78.3±15.4, 15.17±4.9 and the difference was statistically significant (P 0.001,0.001 and 0.002 resp.) and HDL, LDL

Table 3. Correlation of lipid profile with PMD and OSCC (with histological grades)

		N	Mean	Std. Deviation	Statistic	df1	df2	Sig.
Triglyceride -100-150mg/dl	Mild Dysplasia	14	79.36	9.532	12.159	5	26.154	<0.001
	Moderate Dysplasia	6	78.33	15.436				
	Early	23	120.22	23.821				
	Moderately Advanced	7	126.14	31.835				
	Well Differentiated	32	95.91	45.638				
	Moderately Differentiated	18	85	44.775				
	Total	100	98.28	38.513				
Total Cholesterol & Lt;250mg/dl	Mild Dysplasia	14	117.57	7.187	20.495	5	25.036	<0.001
	Moderate Dysplasia	6	125.83	24.49				
	Early	23	156	19.897				
	Moderately Advanced	7	157.57	21.196				
	Well Differentiated	32	142.75	48.657				
	Moderately Differentiated	18	159.11	28.267				
	Total	100	145.24	35.165				
HDL N-40-50 mg/dl	Mild Dysplasia	14	33.14	14.352	0.432	5	24.057	0.822
	Moderate Dysplasia	6	27.33	12.501				
	Very Early	23	31.65	4.052				
	Moderately Advanced	7	32.29	5.122				
	Well Differentiated	32	32.97	4.762				
	Moderately Differentiated	18	32.72	3.77				
	Total	100	32.26	7.182				
LDL -N 100-130	Mild Dysplasia	14	105.5	15.878	1.259	5	25.379	0.312
	Moderate Dysplasia	6	102.33	15.135				
	Very Early	23	106.96	8.647				
	Moderately Advanced	7	114.14	11.231				
	Well Differentiated	32	114.19	34.257				
	Moderately Differentiated	18	114.78	18.463				
	Total	100	110.7	22.673				
VLDL-4-40mg/dl	Mild Dysplasia	14	22.71	13.527	5.123	5	26.331	0.002
	Moderate Dysplasia	6	15.17	4.997				
	Very Early	23	24.22	4.871				
	Moderately Advanced	7	25	6.532				
	Well Differentiated	32	18.5	13.191				
	Moderately Differentiated	18	15.83	8.699				
	Total	100	20.18	10.622				

Table 4. Correlation of lipid profile with gender

	Gender	N	Mean	Std. Deviation	t	df	P Value
Triglyceride -100-150mg/dl	Male	112	99.321	35.3438	1.387	148	0.168
	Female	38	90.947	19.721			
Total Cholesterol & Lt;250mg/dl	Male	112	149.853	31.982	1.16	148	0.248
	Female	38	143.211	25.5778			
HDL N-40-50 mg/dl	Male	112	35	7.63	-1.061	148	0.29
	Female	38	36.5	7.225			
LDL -N 100-130	Male	112	107.69	22.8499	1.086	148	0.279
	Female	38	103.211	19.062			
VLDL-4-40mg/dl	Male	112	20.35	9.7361	1.755	148	0.081
	Female	38	17.484	4.272			

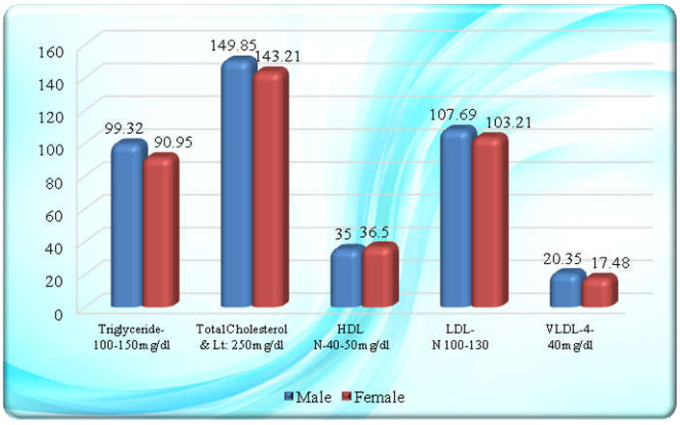
Correlation between lipid profile and OSCC

Correlating the lipid levels with OSCC, the difference was highly significant in smokeless tobacco patients (P <0.001). The overall values of lipid levels were higher in smokeless form of tobacco, but only HDL was significant (P 0.014). (Table 3)

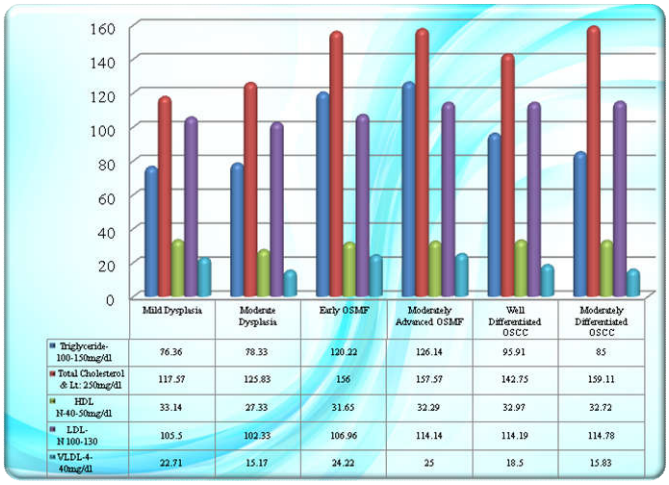
levels were 27.3±15.01, 102.3±15.1 and were statistically nonsignificant (P 0.82,0.31 respectively). (Table 3, graph 2)

Histopathological changes in OSMF

23 patients showed early changes in OSMF. Total cholesterol level was 156±19.8, Triglyceride was 20.2±23.8 and the difference was highly significant (P<0.001). VLDL level was 24.2±4.87 and was significant (P.002).The HDL & LDL levels were 31.65±4.05 and 24.2±4.87 and were nonsignificant (P 0.822 and 0.312). 7 patients showed moderately advanced changes. TC was 157.5±21.1, TG was 126.14±31.8 and VLDL was 25±6.5 and the relation was significant (P 0.001, 0.001 and 0.002). The HDL and LDL levels were 32.2±5.12 and 114.1±11.2 and were non-significant (0.82 and 0.32). (Table 3, graph 2)



Graph 1. Correlation of gender with lipid profile



Graph 2. Correlation of lipid profile with histological grades

Histopathological changes in OSCC

32 patients out of 50 were diagnosed with well differentiated grade. TC was 142.7±48.6, TG was 95.9±45.6, VLDL was 18.5±13.1 and the relation was significant (P <0.001, <0.001 and 0.002). The HDL & LDL levels were 32.2±4.7 and 114.19±34.2 and the relation was nonsignificant (P0.82 and 0.32). 18 patients were diagnosed with moderately differentiated grade. TC was 159.1±28.2, TG was 85±44.7, VLDL was 15.8±8.69 and the relation was significant (P <0.001, <0.001 and 0.002). The HDL & LDL levels were 32.7±3.77 and 114.7±18.4 and the relation was nonsignificant (P0.82 and 0.32). (Table 3, graph 2)

DISCUSSION

Cholesterol and triglycerides are imperative lipid components of cell and are critical in carrying out necessary physiological functions. It is necessary for structural and functional cell integrity. (Martin David, 1986) In cases of malignancy, significant changes in serum cholesterol occur. Because of carcinogenesis, low levels of serum cholesterol in blood and proliferating tissues are noted. Few explanations have been given for association of cholesterol and cancer: low cholesterol even before cancer detection could be result of cancer, cholesterol sets as a marker for cancer detection, may be associated with occurrence of few forms of cancers. (Eichholzer Monika, 2000) Reduced cholesterol may be due to increased lipid membrane biogenesis by cancer cells or direct lipid lowering effect of cancer cells or altered lipid metabolism or antioxidant activity (Choi, 1999). In a study carried out by Patel, Choyu, Schatzkin an inverse relation was seen between head and neck cancers and low serum cholesterol level. This is similar to present study which showed reduced TC and TG in OSCC as compared to controls. A significant decrease in HDL and VLDL was noted in OSCC while an increased LDL was noted in OSCC (Patel, 2004). Alexopolous noted a non-significant decrease in serum TG in controls and other two groups while as in present study the difference was significant (Alexopoulos, 1987).

The present study also compared the lipid levels with form of tobacco consumed and insignificantly increased lipid levels were noted in smokeless tobacco with only HDL showing significant difference. Carcinogens from tobacco cause liberation of free radicals and reactive oxygen radicals which cause high rate of peroxidation of unsaturated fatty acids causing increased utilization of lipids like TG, TC, lipoproteins for membrane biogenesis of cancer cells. The requirements of cell are fulfilled by circulation or synthesized by metabolism or by degradation of lipoproteins like HDL, LDL and VLDL (Choi, 1999). When we correlated histological grading and lipid profile, well differentiated OSCC had low TC, and HDL, moderately differentiated had increased TG, LDL, and VLDL. The present study could be a preliminary study where such a correlation of lipid profile with histologic grades of OSCC was done. However, the difference of HDL & LDL was not statistically significant, so future study which would consider large sample could yield some better difference if at all it prevails.

Conclusion

It is concluded from present study that definite biochemical changes take place in lipid levels in association with OSCC as compared to healthy individuals and these are attributed by increased membrane biogenesis of lipid by these tumor cells.

REFERENCES

Alexopoulos CG, Blatsios B, Avgerinos A. 1987. Serum lipids and lipoprotein disorders in cancer patients. *Cancer*, 60: 3065–70.

Cheng B, Rhodus NL, Williams BA, Griffin RJ. 2004. Detection of apoptotic cells in whole saliva of patients with oral premalignant and malignant lesions: a preliminary study. *J Oral Surg Oral Med Oral Pathol Oral Radiol Endod.*, 97: 465–70.

Choi MA, Kim BS, Yu R. 1999. Serum antioxidative vitamin levels and lipid peroxidation in gastric carcinoma patients. Cancer Lett., 136:89-93.

Chyou PH, Nomura AM, Stemmermann GN, Kato I. 1992. Prospective study of serum cholesterol and site-specific cancers. *J Clin Epidemiol.,* 45:287-92.

Eichholzer Monika, Stähelin Hannes B, Gutzwiller Felix, Lüdin Eric, Bernasconi Florence. 2000. Association of low plasma cholesterol with mortality for cancer at various sites in men: 17-year followup of the prospective Basel study. *Am J Clin Nutr.,* 71:569-74.

Kark JD, Smith AH, Hames CG. 1982. Serum retinol and inverse relation between serum cholesterol and cancer. *Br Med J.,* 284:152-54.

Manoharan S, Kolanjiappan K, Suresh K, Panjamurthy K. 2005. Lipid peroxidation and antioxidants status in patients with oral squamous cell carcinoma. *Indian J Med Res December.,* 122:529-34

Martin David W Jr, Mayes Peter A, Rodwell Victor W. 1986. Granner Daryl K. Harper's review of biochemistry (20th ed). Lange Maruzen publications.

Patel PS, Shah MH, Jha FP, *et al*. 2004. Alterations in plasma lipid profile patterns in head and neck cancer and oral precancerous conditions. *Indian J Cancer.,* 41:25–31.

Schatzkin A, Hoover RN, Taylor PR, Ziegler RG, Carter CL, Albanes D. 1988. Site-specific analysis of total serum cholesterol and incident cancers in the National Health and Nutrition Examination Survey I epidemiologic follow-up study. *Cancer Res.,* 48:452-58.

Sleron A, Adamek M, Kawczk-Krupka A, Mazur S, Ilewicz L. 2003. Photodynamic therapy (PDT) using topically applied delta-aminolevulinic acid (ALA) for the treatment of oral leukoplakia. *J Oral Pathol Med.,* 32: 330–6.

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