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A Study of Serum Lipid Profile in Oral Squamous Cell Carcinoma and its Clinicopathologic Correlation

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ABSTRACT

Background: To evaluate variations in serum lipid profile in patients with oral squamous cell carcinoma (OSCC) and to compare and correlate the serum lipid profile in different clinical stages and histological grades of OSCC.

Materials and Methods: Sixty patients with OSCC and twenty five age and sex matched healthy controls were included in the study. Serum lipid profile including total cholesterol (TC), high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC), very low density lipoprotein cholesterol (VLDLC) and triglycerides were evaluated with the help of a semi-automatic analyzer. Students 't'test and ANOVA were used for statistical analysis.

Results: Statistically significant decrease in levels of serum TC, LDLC, HDLC, VLDLC and triglycerides was observed in cancerous group when compared with the control group.

Conclusion: There are definite variations in the serum lipid profile of OSCC patients. Serum lipid profile might help in evaluation of prognosis and follow-up of OSCC patients.

Keywords: Clinicopathological correlation; oral squamous cell carcinoma; serum lipid profile.

INTRODUCTION

Oral cancer displays difficult and unanswered predicaments for the human population. In western countries, oral cancer accounts for 3-4% of all malignancies. Middle aged and elderly individuals are more commonly affected, with the malignancy being more prevalent among males. In India, 30-40% of all malignancies are oral cancers, due to the habit of chewing and smoking tobacco.[1] Squamous cell carcinomas (SCC) account for 90% of all oral cancers. [2] The World Health Organization has predicted a continuous increase in the incidence of oral cancer worldwide.[3] Oral cancer is a significant problem not only because of the high mortality rate associated with the condition, but also because of the often disfiguring defects and functional loss of tissue associated with treatment.[4] Progress in cancer detection and treatment has not been able to significantly reduce the high mortality rate, and it has the lowest five year survival rate amongst all the major malignant conditions.[5]

The high prevalence and increasing incidence of oral squamous cell carcinoma (OSCC), has necessitated the need of simpler modes for the purpose of screening, diagnosis, therapy and evaluation of prognosis. From this perspective, the biochemical analysis may prove to be of value. Biochemical evaluation of malignancies has shown that during development of tumor there is quantitative alteration of various elements in the serum.[6]Such biochemical elements should be associated with tumor cells and should ideally be

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present in decent quantity in fluid or tissue, for it to be clinically relevant. Analysis of such biochemical elements may determine the appropriate management of an individual patient.

Lipids are components of cell membrane and are essential for biological activities like cell growth and multiplication.[7] Alterations in membrane lipid and/or intracellular lipid has been observed in certain cancer cells. Disturbed cholesterol metabolism and significantly elevated low-density lipoprotein receptors have also been reported in some cancer cells, and these appear to be under internal cellular control. Hence, the metabolism of lipids in cancer cells appears to be different from that in mature normal cells. In addition, the possibility of these lipid variations, and in some instances accumulation of lipids, being intrinsic to proliferation of cells or neoplastic transformation has been raised.[8] The fact that serum lipids play a prominent role in etio-pathogenesis of coronary heart disease is well known. Researchers have documented association of serum lipids and lipoproteins with different malignancies. Variations in serum cholesterol level have been found to be related with the etiology of colorectal and breast cancer.[7] However, only a few studies are reported on the association between serum lipid profile and OSCC. Thus the present study was performed to evaluate serum lipid profile in patients with OSCC and control subjects, and to correlate the serum lipid profile of patients with OSCC with their clinical stages and histopathological grades.

MATERIALS AND METHODS

The present study was conducted in the Department of Oral Pathology and Microbiology, Government Dental College and Hospital, Aurangabad and Department of Biochemistry, Government Medical College & Hospital, Aurangabad. The study was approved by the Institutional Ethics Committee, Government Dental College and Hospital, Aurangabad, India. Written informed consent was obtained from all participants.

Study Population:

The study group comprised of sixty patients with OSCC. The diagnosis of malignancy was confirmed in each case by biopsy and histopathologic examination. A detailed history of each patient was obtained in order to avoid subjects with systemic illness.

Twenty five age and sex matched subjects were selected as control group. A detailed history was recorded to rule out any past or present systemic illness. These subjects were free of any oral tissue abuse habits or any noticeable lesions in the oral cavity. Patients and controls who were obese were excluded from the study.

Clinical Staging:

Clinical staging of the patients with OSCC was done using the TNM classification as given by the American Joint Committee for Cancer staging and End results reporting (AJCCS 1967).[9]

Histopathological Grading:

Incisional biopsies were obtained from the representative site while following all aseptic precautions. The biopsied tissue specimens were fixed in 10% formalin for 24 hours and processed as per the procedure laid down by Bancroft and Stevens (1996).[6] Tissue sections of 5 µm thickness were cut out of each paraffin block. The sections were then stained by haematoxylin and eosin (H&E) stain.

Histopathological grading of OSCC was done according to malignancy grading system proposed by Anneroth G et al (1987).[10] This grading system consists of six morphological characteristics: degree of keratinization, number of mitosis, nuclear polymorphism, stage of invasion, lympho-plasmocytic infiltration and pattern of invasion. Each morphological characteristic was then graded on the basis of points from 1 to 4. As suggested by De Araujo et al (1997)[11] the characteristic of "stage of invasion" was expunged because samples studied were incisional biopsy specimens of OSCC. Mean scores for histopathological grading of malignancy were obtained by dividing the sum of the scores issued to each morphological characteristic by the number of characteristics used. The final grading was done as in Table no. 1.

Collection of blood samples:

Under all aseptic conditions, 2.5 ml of fasting venous blood was drawn from antecubital vein of

Table 1: Histopathology Grading

Total points scored	Grade
1.0 – 2.0	I
2.1 – 3.0	II
3.1 – 4.0	III

Table 2: Comparison of serum lipid profile between control group & OSCC group.

Serum lipid profile	Groups	N	Mean ± SD	't' value	p value (Significance)
TC (mg/dl)	Control	25	187.10 ± 12.7987	7.5510	< 0.0001 S
	OSCC	60	161.08 ± 15.1004		
HDLC (mg/dl)	Control	25	44.61 ± 6.1914	11.1011	< 0.0001 S
	OSCC	60	32.11 ± 3.9884		
TG (mg/dl)	Control	25	115.32 ± 15.2799	3.7779	0.0003 S
	OSCC	60	106.07 ± 7.3256		
LDLC (mg/dl)	Control	25	119.62 ± 13.7142	3.5248	0.0007 S
	OSCC	60	107.76 ± 14.3013		
VLDLC (mg/dl)	Control	25	22.86 ± 3.0387	3.3832	0.0011 S
	OSCC	60	21.21 ± 1.4670		

OSCC patients and control subjects, with the help of a disposable needle and syringe. The blood was allowed to clot at room temperature for one hour in Kahn test tubes. Then the samples were subjected to centrifugation at 3000 rpm for 15 minutes. Thus the serum was obtained for analysis.

Estimation of serum lipid profile:

The serum lipid profile was estimated using kits obtained from Span Diagnostics (Gujarat, India).

Total cholesterol (TC)[12]

Procedure

5 µl of serum sample and 5 µl of cholesterol standard were taken in two Kahn test tubes respectively. 500 µl of cholesterol mono reagent was added to both the tubes. The mixture was kept in incubator at 37˚C for 10 minutes. The absorbance of the standard and sample was measured against the cholesterol mono reagent at 505 nm in a semi-automated analyzer and the reading of total cholesterol (TC) level of sample was recorded.[13]

HDL cholesterol (HDLC)[12]

Principle

Low and Very low-density lipoproteins are precipitated by a solution containing PEG 6000, leaving behind the high-density lipoproteins in the solution. HDL cholesterol is estimated in the supernatant by a series of enzymatic reactions which are initiated by the oxidation of cholesterol to cholestenone by cholesterol oxidase, accompanied by the formation of hydrogen peroxide. In a second reaction catalyzed by peroxidase, 4-aminoantipyrine and phenol react with hydrogen peroxide to form red coloured quinoneimine. Absorbance at 505 nm is directly proportional to HDL cholesterol concentrations[13]

Procedure

100 µl of serum was mixed with 100 µl of precipitating reagent in a Kahn test tube. The mixture was kept at room temperature for 10 minutes. Then it was centrifuged at 2000 rpm for 15 minutes to get a clear supernatant. 50 µl of supernatant and 50µl of HDLC standard were mixed with 500 µl of cholesterol mono reagent in two different Kahn test tubes. Both these mixtures were incubated at 37˚C for 10 minutes. The absorbance of the standard and sample was measured against the cholesterol monoreagent at 505 nm in a semi-automated analyzer and the reading of HDLC concentration of sample was recorded.[13]

Table 3: Comparison of serum lipid profile with clinical stages of OSCC using one way ANOVA.

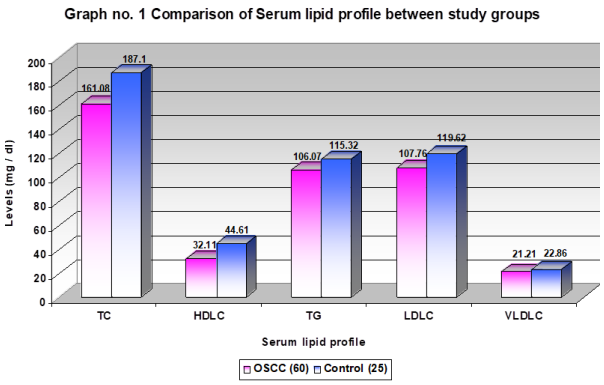
Serum lipid profile	Clinical Stages	N	Mean ± SD	F value	p value (Significance)
TC (mg/dl)	Stage II	9	178.67 ± 13.6649	13.34	< 0.0001 S
	Stage III	22	162.94 ± 10.5791		
	Stage IV	29	154.08 ± 13.7612		
HDLC (mg/dl)	Stage II	9	35.95 ± 4.0166	6.192	0.0037 S
	Stage III	22	31.97 ± 3.5336		
	Stage IV	29	31.02 ± 3.6814		
TG (mg/dl)	Stage II	9	108.75 ± 6.0564	2.119	0.1296 NS
	Stage III	22	103.67 ± 6.6747		
	Stage IV	29	107.05 ± 7.8366		
LDLC (mg/dl)	Stage II	9	120.96 ± 13.6123	8.642	0.0005 S
	Stage III	22	110.42 ± 9.8532		
	Stage IV	29	101.66 ± 14.2958		
VLDLC (mg/dl)	Stage II	9	21.76 ± 1.1958	2.114	0.1301 NS
	Stage III	22	20.74 ± 1.3377		
	Stage IV	29	21.41 ± 1.5720		

Table 4: Comparison of mean serum TC, HDLC and LDLC levels within the various clinical stages of OSCC.

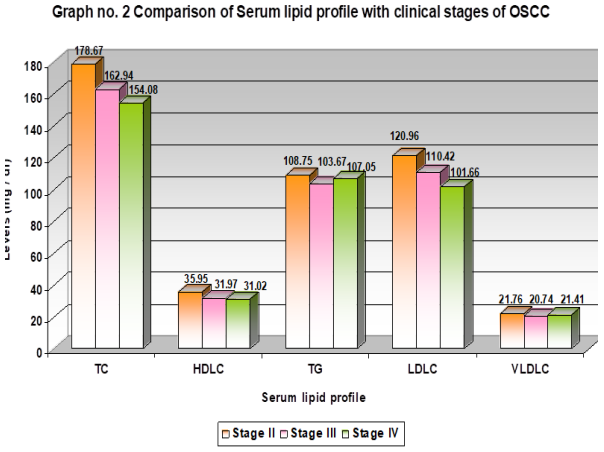
		Stage II vs III	Stage II vs IV	Stage III vs IV
TC (mg/dl)	't' value	3.4526	4.6904	2.5081
	p value (Significance)	0.0017 S	< 0.0001 S	0.0155 S
HDLC (mg/dl)	't' value	2.7395	3.4361	0.9248
	p value (Significance)	0.0104 S	0.0015 S	0.3596 NS
LDLC (mg/dl)	't' value	2.4174	3.5754	2.4618
	p value (Significance)	0.0221 S	0.0010 S	0.0174 S

Table 5: Comparison of serum lipid profile with histopathological grades of OSCC.

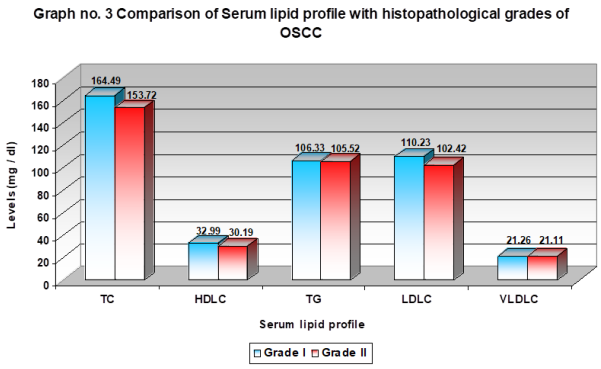
Serum lipid profile	Histological Grades	N	Mean ± SD	't' value	p value (Significance)
TC (mg/dl)	Grade I	41	164.49 ± 13.5938	2.7060	0.0089 S
	Grade II	19	153.72 ± 15.9053		
HDLC (mg/dl)	Grade I	41	32.99 ± 4.1940	2.6612	0.0101 S
	Grade II	19	30.19 ± 2.7165		
TG (mg/dl)	Grade I	41	106.33 ± 7.3625	0.3974	0.6925 NS
	Grade II	19	105.52 ± 7.4137		
LDLC (mg/dl)	Grade I	41	110.23 ± 13.2953	2.0189	0.0481 S
	Grade II	19	102.42 ± 15.2828		
VLDLC (mg/dl)	Grade I	41	21.26 ± 1.4746	0.3878	0.6996 NS
	Grade II	19	21.11 ± 1.4845		



Graph 1: Comparison of serum lipid profile between study groups.



Graph 2: Comparison of serum lipid profile with clinical stages of OSCC.



Graph 3: Comparison of serum lipid profile with histopathological grades of OSCC.

Estimation of triglyceride level[12]

Procedure

5 µl of serum and 5 µl of TG standard were mixed with 500 µl of triglyceride (TG) monoreagent in two different Kahn test tubes. The two tubes were incubated at 37°C for 10 minutes. The absorbance of the standard and sample was measured against the TG monoreagent at 505 nm in a semi-automated analyzer and the reading of triglyceride level of sample was recorded.[13]

Estimation of VLDL cholesterol level[14]

VLDL cholesterol (VLDLC) levels were calculated according to the following formula:

VLDLC = Triglyceride

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Estimation of LDL cholesterol level[14]

LDL cholesterol (LDLC) levels were calculated according to the following formula:

$$LDLC = \text{Total cholesterol} - [\text{HDLC} + \underline{\text{TG}}].$$

Statistical analysis

Evaluation of results and statistical analysis was performed using Student's t-test. The comparison between the clinical stages and histological grades was done using one-way Analysis of Variance. In all the above tests, 'p' value < 0.05 was considered statistically significant.

RESULTS

In the present study, two groups of subjects were studied. First group consisted of 60 patients with OSCC and the second group consisted of 25 healthy control subjects. The OSCC group constituted of 37(61.67%) males and 23(38.33%) females, while the control group consisted of 15(60%) males and 10(40%) females. The age variation was wide, ranging from 31 years to 75 years. The peak incidence of OSCC was noted in the 6th decade.

Clinical staging

Clinical staging was done according to the TNM system (AJCCS, 1967). The present study comprised of 9 cases of OSCC (15%) in stage II, 22 cases (36.67%) in stage III, and 29 cases (48.33%) in stage IV.

Histopathology Grading

Out of the 60 OSCC cases examined, 41 cases (68.33%) were of grade I, while 19 cases (31.67%) were of grade II. There were no cases in grade III oral squamous cell carcinoma.

Results of evaluation of serum lipid profile

The mean serum TC, TG, HDLC, LDLC and VLDLC levels were lower in the OSCC group compared to the control group (Table no.2, Graph no.1). The mean serum TC, TG, HDLC, LDLC, VLDLC levels between OSCC and control group showed a statistically significant difference.

The mean serum TC, HDLC and LDLC levels decreased from stage II to stage IV. There was a statistically significant difference between the different clinical stages of oral squamous cell carcinoma for mean serum TC, HDLC and LDLC levels. The mean serum TG and VLDLC levels did not show any correlation with the clinical stages of oral squamous cell carcinoma (Table no. 3, Graph no.2).

Since the difference of mean values of serum TC, HDLC and LDLC levels between different clinical stages of OSCC were statistically significant, un-paired 't' test was applied to compare the mean values of serum TC, HDLC and LDLC levels within various clinical stages.

It was observed that there is a statistically significant difference in mean value of serum TC and LDLC level for stage II vs stage III, stage II vs stage IV, and stage III vs stage IV. For HDLC, there was a statistically significant difference in mean value of serum HDLC level for stage II vs stage III, stage II vs stage IV, but not for stage III vs stage IV (Table no. 4).

The mean serum TC, TG, HDLC, LDLC and VLDLC levels decreased from grade I to grade II. The difference between mean serum TC, HDLC and LDLC levels for different histopathological grades of OSCC was statistically significant (Table no. 5, Graph no.3).

DISCUSSION

OSCC stands sixth amongst the most common malignancies. It is a major contributor of deaths due to cancer. Worldwide, nearly half a million new oral and pharyngeal malignancies are diagnosed per year, and developing nations account for most of the cases.[15,16] The habit of chewing and smoking tobacco has made OSCC highly prevalent in India.[17]

The chemical nature of cells may shift from normal as they move from normal through premalignant to malignant stage. The metabolism in malignant cells is discrete. Malignant cells bring about alterations in biochemical parameters.[18] Blood acts as a unexampled medium, which displays the different biochemical variations occurring inside the body

due to cancer. Blood based tests are appealing, since they are easy to perform, economical and provide the opportunity of repeating the test.[19]

Cholesterol and triglycerides are important lipid components of cell, vital for carrying out various crucial physiological functions. Cholesterol is necessary for the preservation of the structural and functional integrity of all biological membranes. It is needed for stabilization of DNA helix and is also involved in the activity of membrane bound enzymes. Regulation of cholesterol metabolism and its cellular uptake is mediated by lipoprotein receptors primarily situated on cell surface. Cholesterol and triglycerides are packaged into lipoproteins for their movement in plasma, which are later picked up and consumed by cells in order to fulfill requirements for cellular functions. Cholesterol is an indispensible portion of HDL, LDL, and VLDL. 75% of the serum cholesterol is carried in the form of LDLC.[7]

Some malignant conditions show early and significant variations in serum cholesterol. Carcinogenesis may cause decrease in serum cholesterol levels.[7] Several retrospective and prospective studies have demonstrated an inverse association between serum lipid profile and different malignancies.[20-24] There have been very few reports on serum lipid profile in OSCC.

The present study was carried out to assess serum lipid profile including- 1) TC 2) HDLC 3) TG 4) LDLC and 5) VLDLC levels in patients with OSCC and control subjects. It is an attempt to predict the biological role of serum lipid profile as a biochemical parameter in patients with OSCC. Biochemical analysis for the estimation of serum lipid profile was carried out with the help of a semi-automated analyzer. The method for estimation of serum lipid profile was standardized and was preferred since this method proved to be accurate, quick, economical and was widely used.

The present study noted a decrease in the mean serum TC, TG, HDLC, LDLC and VLDLC levels of patients with OSCC when compared to controls and the difference was statistically significant. Chyou P et al [25], noticed an inverse trend between head and neck malignancies and lower serum total cholesterol. Patel PS et al [7] observed statistically significant decrease in the levels of TC, TG, HDLC, and VLDLC levels in head and neck cancer patients when compared to controls. They noted a decline in LDLC levels of patients as compared to controls but the difference was not statistically significant. It was suggested that the decreased levels of serum cholesterol and other lipid components in oral cancer patients may be because of their heightened employment by cancer cells for genesis of new membranes. Body cells obtain cholesterol mainly from LDL portion of lipoproteins. This might account for the decrease in the LDLC levels in OSCC patients, noted in the present study. Alexopoulous CG et al [20] have observed insignificant difference in serum TG between cancer patients and controls. Thompson MP et al [26] have recorded an elevation in the activity of lipoprotein lipase in tumors. This may result in an increase in free fatty acids in circulation which may add to decrease in triglyceride level.

Rapid cell proliferation may lead to cholesterol esters being captured inside cells probably to fulfill the increased need of cholesterol for new membrane genesis taking place during proliferation of cells.[14] Gebhard RL et al [27] suggested that free cholesterol within the tumor cells, whether originating from uptake or synthesis, is preferentially channeled into storage as cholesteryl ester via ACAT instead of being discharged by the cells to circulatory HDL. This results in decrease in HDLC levels in malignancy.

The present study recorded lesser TC levels as compared to Chyou P et al.[25] Chyou P et al [25] studied the TC levels of oral and pharyngeal cancers combined. In addition, the study included cases other than SCC as well, and it was conducted on Japanese-American men. The mean serum HDLC, LDLC and VLDLC levels in the present study were in accordance with the results of Patel PS et al.[7] We also observed comparatively lower TC and higher TG levels as compared to that recorded by Patel PS et al.[7] The study by Patel PS et al [7] included cases of malignancies of pharynx, larynx and maxilla along with OSCC. Histologically 174 patients represented SCC, the remaining 10 cases were malignancies other than SCC. In addition, their study had cases of poorly differentiated and of undifferentiated malignancies. In present study, there were 41 cases of grade I and 19 cases of grade II OSCC. These factors might account for the

variation in the TC and TG levels between the present study and that by Patel PS et al.[7]

In the current study, the values of serum lipid profile were correlated with the different clinical stages and histopathological grades of OSCC. It was evident that the mean serum TC, HDLC and LDLC levels correlated with the clinical grades of OSCC and the difference was found to be statistically significant ($p < 0.05$). On application of unpaired 't' test, it was observed that the difference of mean values of serum TC and LDLC levels were significant for stage II vs stage III, stage II vs stage IV and stage III vs stage IV. For HDLC, the difference of mean values was significant for stage II vs stage III and stage II vs stage IV, but not for stage III vs stage IV.

Scolozzi R et al [28] observed an inverse association between levels of TC and the clinical stage and M component in forty one patients suffering from multiple myeloma. In a study on 202 patients affected by various hematological malignancies, Marini A et al observed an inverse relationship between TC level and clinical stage in non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphatic leukemia.[29] Halton JM et al [24] in study on acute lymphatic leukemia in children observed that the cholesterol and HDLC levels were lower in children with widespread disease than in children with localized tumours. In the present study, majority of patients belonged to stage IV of OSCC, followed by stage III. There were no cases of stage I OSCC. Most of the patients reported to the institute in an advanced stage because of ignorance and lack of awareness. The decline in serum TC, HDLC and LDLC levels observed with increasing clinical stage shows that an increase in tumor burden might cause a decrease in these lipid profile parameters. The mean serum TG and VLDLC levels amongst the different clinical stages of OSCC were not statistically significant ($p > 0.05$). The available literature did not present any data regarding comparison of serum lipid profile and clinical stages of OSCC, hence comparison with reported literature was not possible.

The mean serum TC, HDLC and LDLC levels correlated well with the histopathological grades of OSCC and the difference was observed to be statistically significant ($p < 0.05$). Though the mean serum TG and VLDLC levels (mg/dl) were lower in grade II (105.52 ± 7.4137 and 21.11 ± 1.4845 respectively) compared to grade I OSCC (106.33 ± 7.3625 and 21.26 ± 1.4746 respectively), the difference was not statistically significant ($p > 0.05$). The available literature did not reveal any study in which correlation between serum lipid profile and histopathological grades was done. Hence comparison with reported literature was not possible.

According to Vitols S et al [30], hypocholesterolaemia in malignant conditions may be due to elevated LDL-receptor activity in the cancer cells. LDL receptors are essential for metabolizing circulating LDLC levels and almost 80% of the plasma LDLC is cleared by LDL receptors. A single LDL particle is composed of a polar shell of phospholipids, protein and free cholesterol surrounding nearly 1500 cholesteryl ester molecules. The protein portion of LDL collaborates with specific cell-surface receptors. Once bound to the receptors, LDL is debased in lysosomes and cholesterol is discharged which is then used in various functions, including membrane genesis. Accordingly, it was suggested that the huge consumption and degradation of LDL by cancer cells may be utilized to target malignant cells with chemotherapeutic agents bound to LDL.

CONCLUSION

The decreased serum lipid profile may be applied as an adjunct in diagnosis, for forecasting the prognosis and also predicting the response to therapy along with other diagnostic aids. However, further exhaustive studies are needed to confirm their utility in evaluating the premalignant to malignant stage condition.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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