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Analysis of lipid profile in cancer patients, smokers, and nonsmokers

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ABSTRACT

Background: Lipids play an important role in maintaining the cell membrane integrity. Lipid profile is a panel of blood tests that serve as an initial medical screening for abnormalities in lipids and approximate risk for cancer, cardiovascular diseases, pancreatitis, etc., The present study evaluates the alterations in lipid profile in cancer patients, smokers, and nonsmokers and aims to achieve a correlation between them.

Materials and Methods: The study is an *in vitro* type of cross-sectional study with 25 oral cancer patients, 25 chronic smokers (habit persisting for 15 years or more), and 15 nonsmokers as control group. Blood samples had been collected, and triglycerides (TGs), total cholesterol (TC), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) were analyzed using a lipid profile kit and an autoanalyzer. The results were analyzed using the unpaired *t*-test and ANOVA test ($P < 0.05$).

Results: There was a significant increase in TC, TG, LDL, and VLDL and decrease in HDL in the smokers group when compared to the controls ($P < 0.05$). A significant increase in LDL, but a decrease in values of HDL, VLDL, TG, and TC was observed in the cancer patients group when compared to the controls ($P < 0.05$).

Conclusion: There is an inverse relationship between serum lipid profile in smokers and cancer patients. The decrease in lipid profile in cancer patients might be due to their increased utilization of lipids by neoplastic cells in membrane biogenesis. Therefore, a decrease in lipid profile in smokers can be assumed that they might be more prone to develop cancerous conditions.

Key Words: Carcinogenesis, cell membrane, cholesterol LDL, cholesterol HDL, lipid metabolism, lipoproteins, liver, risk factors, smoking

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INTRODUCTION

Tobacco is the single greatest cause of preventable death globally.[1] Tobacco use leads most commonly to diseases affecting the heart, liver, and lungs, with smoking being a major risk factor for heart attacks, strokes, chronic obstructive pulmonary disease (including emphysema and chronic bronchitis), and cancer (particularly lung cancer, cancers of the larynx and mouth, and pancreatic cancer). It also causes peripheral vascular disease and hypertension.[2] Smoking is thus a potential threat to the present and the future generations. The World Health Organization estimates that tobacco caused 5.4 million deaths in

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2004[3] and 100 million deaths over the course of the 20th century.[4] Similarly, the United States Centers for Disease Control and Prevention describes tobacco use as "t he single most important preventable risk to human health in developed countries and an important cause of premature death worldwide."[5] By 2030, if similar trends in cigarette smoking continue, it will kill more than 9 million people annually.[6]

Smoking cigarette/beedi is a dominant risk factor for premature or accelerated peripheral, coronary, and cerebral atherosclerotic vascular disease. Smoking tends to increase blood cholesterol levels. Furthermore, the ratio of high-density lipoprotein (HDL) (the "good" cholesterol) to low-density lipoprotein (LDL) (the "bad" cholesterol) tends to be lower in smokers compared to nonsmokers.[7]

Tobacco use accounts for at least 30% of all cancer deaths, causing 87% of lung cancer deaths in men and 70% of lung cancer deaths in women. Besides lung cancer, tobacco use also increases the risk for cancers of the mouth, lips, nose and sinuses, larynx, pharynx, esophagus, stomach, pancreas, kidney, bladder, uterus, cervix, colon/rectum, and ovary.[8] Uncontrolled cell proliferation, impaired cell apoptosis, and differentiation are the hallmarks in tumorigenesis. An altered lipid profile has been associated with cancer[9-11] though the exact pathogenesis of cancer is not reaffirmed as its prime role in pathogenesis of coronary heart disease. These studies tested the alteration in lipid profile in cancer (head and neck squamous cell carcinoma) and precancerous conditions and found a reduced lipid profile in head and neck squamous cell carcinoma patients. The aim of the present study is to demonstrate the effect of smoking on lipid profile in smokers, nonsmokers, and oral cancer patients.

MATERIALS AND METHODS

In this cross-sectional study, three groups, namely, oral cancer patients, smokers, nonsmokers as controls were evaluated for lipid profile. Lipid profile is an appealing investigation procedure in terms of its ease, economic advantage, and possibility of repeated sampling. Institutional ethical clearance was obtained (GPRDCH/IEC/2014/021).

A detailed case history, clinical examination of the oral cavity of all the patients was done. The study group consisted of 25 patients with histologically confirmed oral squamous cell carcinoma who had a habit of smoking for more than 15–20 years. The next group consisted of 25 smokers who had the habit of smoking for 15 years or more. The control group consisted of 15 nonsmokers who were age- and sex-matched without any history of smoking or major illness in the past. Exclusion criteria were patients with uncontrolled diabetes, liver dysfunction, or thyroid disorders. The 65 subjects were included in the study, belonged to an age group of 40–70 years and most of them were males.

The lipid profile test is a panel of serum total cholesterol (TC), serum triglyceride (TG), HDL, LDL, very LDL (VLDL). Five milliliters of fasting blood sample (8–10 h) was collected under aseptic conditions. The sample was centrifuged at 200 rpm for 1 min to separate the serum [Figure 1]. The serum was then analyzed for lipids using the commercially available working reagents (Excel Diagnostics, Hyderabad, India) for lipids [Figure 2]. About 0.05 ml of serum sample to 1 ml of working reagent was mixed and incubated at 37°C and analyzed using an autoanalyzer which works on colorimetric principle [Figure 3].

Statistical analysis

Tabulation of results was done for the oral cancer patients, smokers, and nonsmokers groups. All the variables were statistically analyzed for the mean values, standard deviation, standard error range, and *P* value. Statistical analysis was done using the standard ANOVA test and unpaired *t*-test. In all the above tests, $P < 0.05$ was taken to be statistically significant; $P > 0.05$ was not significant.

RESULTS

Table 1 shows the comparison between the smokers and nonsmokers or the control group. An increase in the serum cholesterol, TGs, LDL, and VLDL can be seen in the smokers group when compared to the nonsmokers, with a decrease in HDL ($P < 0.05$).

Table 2 shows the comparison between the cancer patients and nonsmokers as the control group. A decrease in serum cholesterol, TGs, LDL, and VLDL can be observed in cancer patients, with an increase in HDL ($P < 0.05$).

Table 3 shows the comparison between the cancer-smokers and non-cancer smokers. The *P* value is significant.

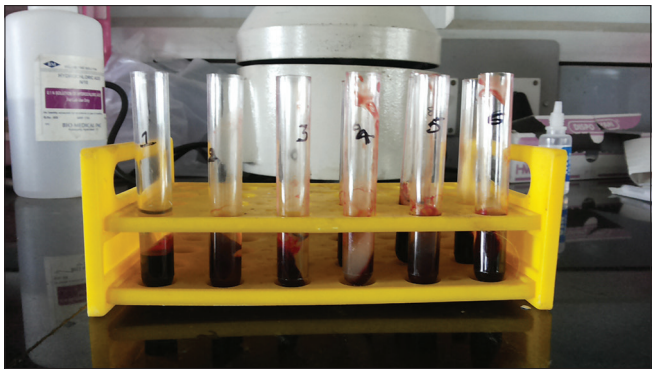

Figure 1: Patient's fasting blood sample has been collected and centrifuged to separate the serum.

Figure 2: Commercially available lipid profile reagents have been used to mix with the serum sample.

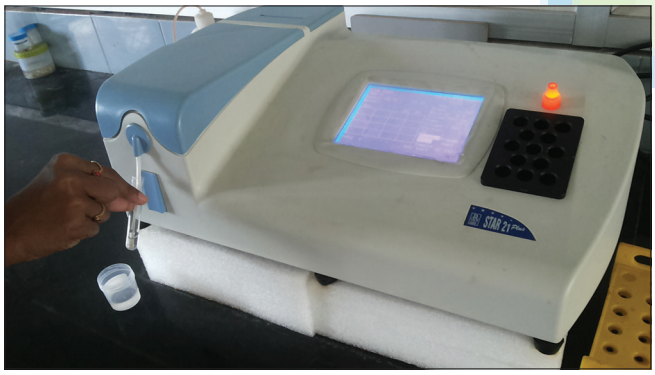

Figure 3: The incubated serum sample with lipid reagent is analyzed for lipid levels using an autoanalyzer.

DISCUSSION

Lipid profile is a panel of tests consisting of five main parameters, TC, total TG, HDLs, LDLs, and VLDLs. Cholesterol is an important sterol of the body required for the biogenesis of the cell membranes and to maintain the physiologic fluidity of the membrane across a range of temperatures.[12] The normal mean serum cholesterol level is 118.4 ± 32 mg/dl. Serum cholesterol level above or below the normal range is of concern. The mean cholesterol level in smokers in our study is 183.32 mg/dl which is high above the

Table 1: Comparison of lipid profile between smokers and nonsmokers or the control group

Lipid profile parameters	Groups	*n*	Mean	SD	SEM	*P*
Cholesterol	Control	15	98.4000	19.64252	5.07168	0.000
	Smokers	25	183.3200	42.58983	8.51797	
LDL	Control	15	54.2747	12.34699	3.18798	0.000
	Smokers	25	117.3884	33.11308	6.62262	
Triglycerides	Control	15	128.2000	15.30266	3.95113	0.000
	Smokers	25	290.5600	108.98818	21.79764	
VLDL	Control	15	25.6400	3.06053	0.79023	0.000
	Smokers	25	58.1120	21.79764	4.35953	
HDL	Control	15	23.8107	2.83168	0.73114	0.000
	Smokers	25	8.8196	2.77259	0.55452	

LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; HDL: High-density lipoprotein; SD: Standard deviation; SEM: Standard error of mean

Table 2: Comparison of lipid profile between cancer patients and nonsmokers as the control group

Lipid profile parameters	Groups	*n*	Mean	SD	SEM	*P*
Cholesterol	Cancer	25	91.9600	33.13040	6.62608	0.048
	Control	15	98.4000	19.64252	5.07168	
LDL	Cancer	25	71.1788	25.95958	5.19192	0.024
	Control	15	54.2747	12.34699	3.18798	
Triglycerides	Cancer	25	126.2800	32.91469	6.58294	0.033
	Control	15	128.2000	15.30266	3.95113	
VLDL	Cancer	25	25.2560	6.58294	1.31659	0.038
	Control	15	25.6400	3.06053	0.79023	
HDL	Cancer	25	20.5988	6.48278	1.29656	0.045
	Control	15	23.8107	2.83168	0.73114	

LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; HDL: High-density lipoprotein; SD: Standard deviation; SEM: Standard error of mean

Table 3: Comparison of lipid profile between the cancer patients and smokers

Lipid profile parameters	Groups	*n*	Mean	SD	SEM	*P*
Cholesterol	Cancer	25	91.9600	33.13040	6.62608	0.000
	Smokers	25	183.3200	42.58983	8.51797	
LDL	Cancer	25	71.1788	25.95958	5.19192	0.000
	Smokers	25	117.3884	33.11308	6.62262	
Triglycerides	Cancer	25	106.2800	32.91469	6.58294	0.000
	Smokers	25	290.5600	108.98818	21.79764	
VLDL	Cancer	25	15.1560	6.58294	1.31659	0.000
	Smokers	25	58.1120	21.79764	4.35953	
HDL	Cancer	25	18.5988	6.48278	1.29656	0.000
	Smokers	25	8.8196	2.77259	0.55452	

LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; HDL: High-density lipoprotein; SD: Standard deviation; SEM: Standard error of mean

normal levels. These values are in accordance with the studies conducted by Sinha *et al*.[13] and Khurana *et al*.[14] The increased cholesterol levels in the blood is quite troublesome as hypercholesterolemia promotes atheroma development in arteries leading to atherosclerosis. This disease process leads to myocardial infarction, stroke, and peripheral vascular disease.[15]

In our study, smokers showed an increase in LDL, TG, and VLDL and a decreased HDL all of which are measures of the deteriorating health condition. Our results were in synchrony with the studies conducted by Guedes *et al*.[16] and Sliwinska-Mosson *et al*.[17] Lipoproteins, in order of molecular size, largest to smallest, are chylomicrons, (VLDL), intermediate-density lipoprotein, LDL, and HDL. Lipoproteins are complex particles composed of multiple proteins which transport all fat molecules (lipids) around the body within the water outside cells.[18] The fats carried include cholesterol, phospholipids, and TGs; amounts of each which are quite variable. LDL is one of the five major groups of lipoproteins. LDL particles are referred to bad cholesterol as LDL particles pose a risk for cardiovascular disease. Atherosclerosis is initiated by an inflammatory processes in the endothelial cells of the vessel wall in response to retained LDL particles.

Lipoproteins in the blood vary in size. LDL particles are formed as VLDL lipoproteins lose TG through the action of lipoprotein lipase (LPL) and they become smaller and denser (i.e. fewer fat molecules with same protein transport shell), containing a higher proportion of cholesterol esters. Some data suggest that small dense LDL particles are more prone to pass between the endothelial cells, going behind the cellular monolayer of endothelium. LDL particles and their contents are more susceptible to oxidation by free radicals and the risk is higher while the particles are in the wall than while in the bloodstream. Once inside the vessel wall, LDL particles can become more prone to oxidation. Endothelial cells respond by attracting monocyte white blood cells, causing them to leave the blood stream, penetrate into the arterial walls, and transform into macrophages. The macrophages' ingestion of oxidized LDL particles triggers a cascade of immune responses which overtime can produce an atheroma if HDL removal of fats from the macrophages does not keep up. The immune system's specialized white blood cells (macrophages and T-lymphocytes) absorb the oxidized LDL, forming specialized foam cells. If these foam cells are not able to process the oxidized LDL and recruit HDL particles to remove the fats, they grow and eventually rupture, leaving behind cellular membrane remnants, oxidized materials, and fats (including cholesterol) in the artery wall, forming plaques which eventually rupture leading to thrombus and myocardial infarction.

HDL is thus termed as good cholesterol because they can transport cholesterol and TGs out of artery walls, reduce macrophage accumulation, and thus help prevent, even regress atherosclerosis over weeks, years, decades, thereby helping prevent cardiovascular disease, stroke(s), and other vascular disease complications.

In our study, the cancer patients showed a decrease in cholesterol, TGs, HDL, and VLDL with an increase in LDL compared to control group. This was in accordance with the study conducted by Acharya *et al*.,[19] Garg *et al*.,[10] Li *et al*.,[9] Lohe *et al*.,[12] Kumar *et al*., Ghosh *et al*.,[20] and Patel *et al*.[21] Lower lipid profile levels have been associated in a variety of cancers ranging from head and neck to pancreatic cancers.[22] The main hallmark of cancer is uncontrolled and unwanted proliferation of cells leading to tumor formation.[21] The cell membrane is made up of lipoproteins. Thus, the body lipids are used for the biogenesis of the cell membranes of the newly forming neoplastic cells and this causes a decrease in the cholesterols, TGs, and lipoproteins in the cancer patients. Various hypotheses have been put forward to explain the lowered cholesterol levels in cancer. First, lower cholesterol values, even before the manifestation or detection of cancer, may be a result of the cancer process; second, lower cholesterol values may precede the development of cancer, but the association with cancer is secondary which indicates that cholesterol serves as a marker for some other causal variable or set of variables; third, lower cholesterol values may precede the development of cancer and may be causally associated with the occurrence of some forms of cancer. Williams *et al*. mentioned that one of the postulated mechanisms for the lower level of serum cholesterol in cancer patients is that there is an increased membrane permeability to carcinogens induced by trans-fatty acids.[23] According to Patel *et al*. 66% higher mortality rate has been observed in cancer patients with lower plasma cholesterol levels when compared to the higher plasma cholesterol levels.[21] However, few studies have reported that hypolipidemia may result because

of the direct lipid lowering effect of tumor cells or some secondary malfunction of the lipid metabolism or secondary to antioxidant vitamins. It is widely demonstrated that oral cancer interferes significantly on food intake as well as on lipid ingestion and absorption. Therefore, it can be expected that patients with oral cancer have low serum levels of lipids, but the other factors, such as genes and hormones, also interact to regulate the plasma cholesterol levels in human. A recent addition is that lipid peroxidation may play an important role in cancer development as lipid peroxidation product, malondialdehyde, may cross-link DNA through adenosine and cytosine.[24] This cross-linking may result in carcinogenesis and mutagenicity.

An important finding in our study is the increased levels of LDL in the serum of our 25 oral cancer patients (whereas HDL, VLDL, TG, TC decreased). LDL, as we know, is increased in the smokers. An increase was also seen in the oral cancer patients, but it was not a very significant increase as seen in smokers. Since LDL is more susceptible to oxidation, its higher peroxidation occurs during oxidative stress which results in generation of free radicals leading to lipid peroxidation and mutagenicity. In our study, 25 oral cancer patients had the habit of smoking for 15 years or more. An increased LDL activity in tumor cells may produce hypocholesterolemia. Therefore, LDL can be used as a mediator between smoking and occurrence of cancer. In our study, all the patients had the habit of smoking for more than 15 years and above, with this we may correlate that the habit of smoking for more than 15 years or more may affect the serum lipid profile by a gradual decrease and the mucosa turns from normal to premalignant or malignant conditions and the lipid profile may decrease further. However, our study included only smokers with the habit of smoking >15 years, it does not show the effects of smoking on lipid profile when the habit was <15 years. Therefore, in future, research should be done if smoking for <15 years could have any substantial effect on lipid profile and oral cancer.

CONCLUSION

The results of our present study show that there is an increase in lipid profile in smokers, whereas an inverse relation can be observed in oral cancer patients. Thus, a decreasing serum lipid status in the chronic smokers, especially the LDL can be used as an early indicator for changes in the neoplastic cells. However, a detailed study of cholesterol-carrying lipoprotein transport and the efficiency of the receptor system may help in understanding the underlying mechanisms of regulation of plasma cholesterol concentration in cancer. This is a short study and further extension of the study to observe the lipid profile in precancerous conditions and smokers with the habit of smoking for more than 15 years and above is required for a definitive conclusion.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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