Alterations in Serum Lipid Profile Patterns in Oral Cancer: Correlation with Histological Grading and Tobacco Abuse

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Abstract

Albeit alterations in serum lipid profile patterns have long been associated with malignancies, still role of these alterations remains controversial. It has been suggested a causative relationship might exist between plasma lipid levels and oral cancer patients. Further, the habit of tobacco consumption is on the rise and most often the oral cancer patients are afflicted with this menace. As a matter of fact, tobacco contains carcinogens capable of damaging the cell membrane components including lipids. Thus, the purpose of the present review is to discuss the basics of lipids and to evaluate alterations in plasma lipid profile in oral cancer patients and its association with histological grading and tobacco abuse. Pertinent literature was searched in PubMed and Medline by using key words such as serum lipid profile, oral cancer, histological grades and tobacco abuse.

Key words: Histological grades, Lipids, Oral cancer, Serum lipid profile, Tobacco abuse

Introduction

Oral Cancer (OC) is the sixth most common cancer in the world [1]. Despite intensive efforts throughout the world, cancer still remains an enigma. Head and neck cancer accounts for 30- 40% of all malignant tumors in India and the most common malignant neoplasm is Oral Squamous Cell Carcinoma (OSCC) [2]. The incidence & mortality rate of OC is still unacceptably high [3]. By the time it is diagnosed, OC often is far advanced and deadly. These deaths are particularly tragic because, in most cases, they can be prevented with early diagnosis and treatment [4]. Early detection of these lesions can dramatically improve the treatment outcome and prognosis in such patients. Carcinoma development is a complex mechanism comprising of proliferation, apoptosis and differentiation and the interplay between these intricate processes decides tumor development and progression [5]. Thus, the development of newer diagnostic and predictive approaches that are safe, economical, and amenable to repeated sampling is imperative. Blood-based/serum-based tests offer the aforementioned advantages [6].

Fundamentally, the newly proliferating tumor cells would need many basic components well above the normal limits, used in physiological process. One such component is lipids which form major cell membrane components essential for various biological functions including cell division and growth of normal and malignant tissues. The increased requirement of lipids to fulfill the need of these new cells would be expected to diminish the existing lipid stores [6]. Although their prime role in pathogenesis of cardiovascular disease has been consistently found, researchers have reported an association of serum lipids with different cancers [7-13]. However, only a few reports are available on plasma lipid profile in head and neck cancers [7,11,13,14]. The question of whether hypolipidemia at the time of diagnosis is a causative factor or a result of cancer has remained unanswered [11].

The purpose of the present review is to throw a light on the basics of lipids and also to evaluate alterations in plasma lipid profile in oral cancer patients and its association with histological grading and tobacco abuse, thus assisting in better understanding of these complex phenomenona.

Definition of Lipids

It is customary to define lipids in terms of their solubility in certain organic solvents, the presence of esterified fatty acids, and their utilization by living organisms. Since for each of these criteria there can be found exceptions, undue stress should not be put on a simple definition [15]. Basically lipids are defined as 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 [16-31]. Lipids may also be defined as hydrophobic or amphiphilic small molecules; the amphiphilic nature of some lipids allows them to form structures such as vesicles, liposomes, or membranes in an aqueous environment [32].

Classification of Lipids

Lipids can be classified based on their composition and the functions they perform (*Figure 1*) [15-22,24,26,28,29,31-33]. On the basis of their composition, lipids are broadly classified into simple lipids (esters of fatty acids with alcohol; these include fats, waxes), complex lipids (esters of fatty acids with alcohols containing additional groups such as phosphate, nitrogenous base, carbohydrate, protein etc.; these include phospholipids, non-phosphorylated lipids, lipoproteins, sulfolipids), and derived lipids (derivatives obtained on the hydrolysis of simple and complex lipids which possess the characteristics of lipids; these include eicosanoids, isoprenoids, fat soluble vitamins, steroids, ketone bodies, fatty acids). On the basis of their function, lipids are broadly

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classified as storage lipids (fats, oils), structural lipids (phospholipids, non-phosphorylated lipids), and lipids as signals, cofactors and pigments (phosphatidylinositol, eicosanoids, steroid hormones, fat soluble vitamins, lipid quinines, dolichols).

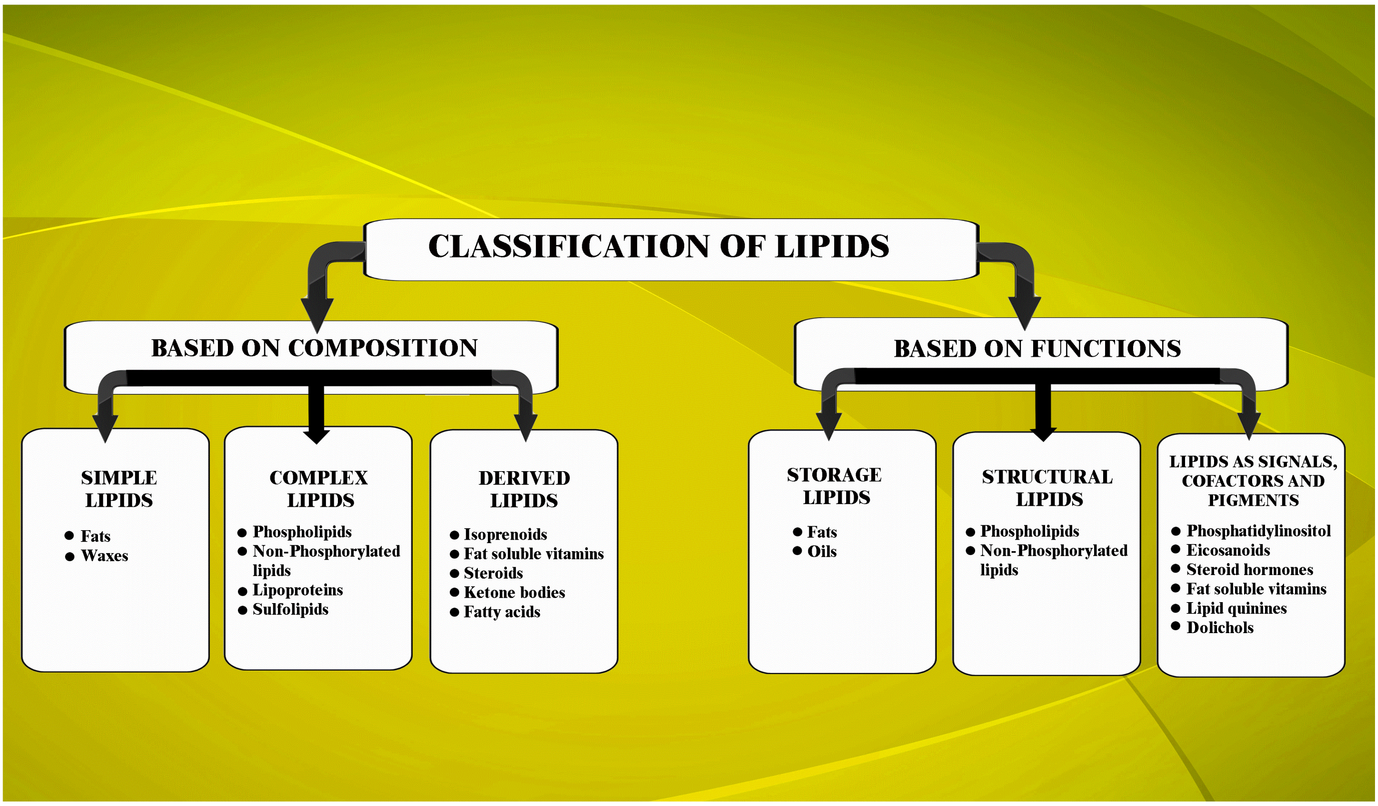

Figure 1. Classification of lipids based on their composition and the functions they perform.

Lipid Metabolism in Physiology [29,32,34]

Digestion of lipids in oral cavity, stomach and small intestine

Most of the dietary lipid is in the form of triglycerides, cholesterol, and phospholipids. The digestion of lipids is initiated in the oral cavity by the action of enzyme lingual lipase, with diglycerides being the primary reaction product. The digestion of lipids in the stomach is almost negligible, because of lack of emulsification and low pH, thus creating an unfavorable environment for the action of gastric lipase. In the small intestine emulsification takes place by three complementary mechanisms: detergent action of bile salts; surfactant action of degraded lipids; mechanical mixing due to peristalsis. This disperses lipids into smaller droplets due to reduction in the surface tension and an increase in the surface area of lipid droplets. The pancreatic enzymes are primarily responsible for the degradation of dietary triacylglycerols, cholesteryl esters and phospholipids. Pancreatic lipase cleaves triacylglycerols to produce 2-monoacylglycerol and free fatty acids. Pancreatic cholesterol esterase cleaves cholesteryl esters to produce cholesterol and free fatty acids. Phospholipids undergo hydrolysis by the action of pancreatic phospholipases.

Absorption and transport of lipids

Bile salts act as biological detergents, converting dietary fats into mixed micelles of bile salts and triacylglycerols, thereby exerting a solubilizing effect on the lipids. The products of lipase action i.e. monoacylglycerols, diacyl-glycerols, free fatty acids, and glycerol diffuse into the epithelial cells lining the intestinal surface. In the cells of intestinal mucosa, long chain fatty acids are reconverted into triacylglycerols by the action of enzymes thiokinases and acyl transferases. The resynthesized lipids form lipoprotein aggregates called chylomicrons, which move from the intestinal mucosa into the lymphatic system by exocytosis from which they enter the blood and are carried to muscle and adipose tissue. In the capillaries of these tissues, the extracellular enzyme lipoprotein lipase, activated by apoC-II, hydrolyzes triacylglycerols to fatty acids and glycerol. These fatty acids and glycerol are taken up by cells in the target tissues. In muscle, the fatty acids are oxidized for energy whereas in adipose tissue, they are reesterified for storage as triacylglycerols.

When the diet contains more fatty acids than are needed immediately for fuel or as precursors, the liver converts them to triacylglycerols, which are packaged with specific apolipoproteins into Very Low Density Lipoprotein Cholesterol (VLDL-C). The VLDL-Cs are transported in the blood to muscle and adipose tissues. In the adipose tissue, the triacylglycerols are removed and stored in lipid droplets within adipocytes, whereas in muscle fatty acids are oxidized to supply energy. The loss of triacylglycerols converts some VLDL-C to VLDL-C remnants, also called Intermediate Density Lipoprotein Cholesterol (IDL-C), and with further removal of triacylglycerol to Low-Density Lipoprotein Cholesterol (LDL-C). LDL-Cs carry cholesterol to extrahepatic tissues that have specific plasma membrane receptors for LDL-C. These receptors mediate the uptake of cholesterol and cholesteryl esters. High Density Lipoprotein Cholesterol (HDL-C) mediates the transport of excess cholesterol in extrahepatic tissues back to the liver. The various steps of lipid metabolism have been summarized in *Figure 2*.

Lipid Metabolism and Lipid Profile Patterns in Oral Cancer

Lipids in malignant tumors are not only necessary for providing the membrane constituents of proliferating cells but are also needed for energetic, biophysical and signaling pathways that drive tumorigenesis. Dysregulated lipid metabolism is a hallmark of cancer [35]. Cancer specific modifications of the lipid metabolism can affect the production of specific signaling lipids, such as factors derived from poly-unsaturated fatty acids and alter the availability of specific Fatty Acids (FA) pools required for protein modification [36].

Furthermore, researchers have been intrigued in recent years with the possible role of dietary and endogenous lipids in the etiology and prognosis of cancer. Cholesterol, which is recognized to be important factor in the etiology of coronary heart disease, has recently become the focus of attention on the possible role in the etiology of cancer. There is a consistent surge of studies showing an increased mortality in cancer subjects with low plasma cholesterol levels [37,38]. There exists a controversy that hypocholesteremia is a predisposing factor for cancer development [39-42], or hypocholesteremia is in fact the result rather than the cause of cancer [39,43,44]. Current theories regarding cancer causation have generated interest in variables such as levels of serum cholesterol and triglycerides as potential associations with cancer relating to dietary factors or basic constitutional factors [39,45,46].

Cancer tissues are able to synthesize lipids de novo and it has also been demonstrated that the amount of lipid synthesis in cancer tissue is comparable to liver [47]. It has been shown that adipocytes promote homing, migration and invasion of cancer cells. They sustain cancer metastases by providing energy for rapid tumor growth. Furthermore, co-culture of adipocytes and cancer cells demonstrate transfer of lipids from adipocytes to cancer cells, enhanced lipolysis in adipocytes and elevated β-oxidation in cancer cells [48].

De novo lipogenesis is considered to be the primary source of fatty acids available for lipid synthesis in cancer cells. However, cancer cells do not solely rely on de novo lipogenesis but also utilize exogenous fatty acids for membrane synthesis and for the synthesis of oncogenic signaling lipids such as ceramide-1-phosphate, platelet activating factor, diacylglycerol and lysophosphatidic acid [49-51]. the importance of lipid metabolism in cancermechanisms[36].

It has been consistently observed that in some malignant diseases, blood cholesterol undergoes early and significant changes. Cholesterol and Triglycerides (TGL) are important lipid constituents of the cell and are essential to carry out several vital physiological functions. Cholesterol is essential for maintenance of the structural and functional integrity of all biological membranes. It is also involved in the activity of membrane-bound enzymes and is important for stabilization of the DNA helix. Several prospective and retrospective studies have shown an inverse association between blood lipid profile and different cancers [8,10,11,13,52-54]. Lohe et al. have observed an inverse relationship between serum lipid profile and oral cancer and oral precancer [12]. Patel et al. have also observed an inverse relationship between lower plasma lipid profile and head and neck malignancies and oral precancerous conditions [11,13]. Furthermore, some investigators have also found a relation of low serum cholesterol with increased risk of cancer occurrence and mortality [11,12,55-58].

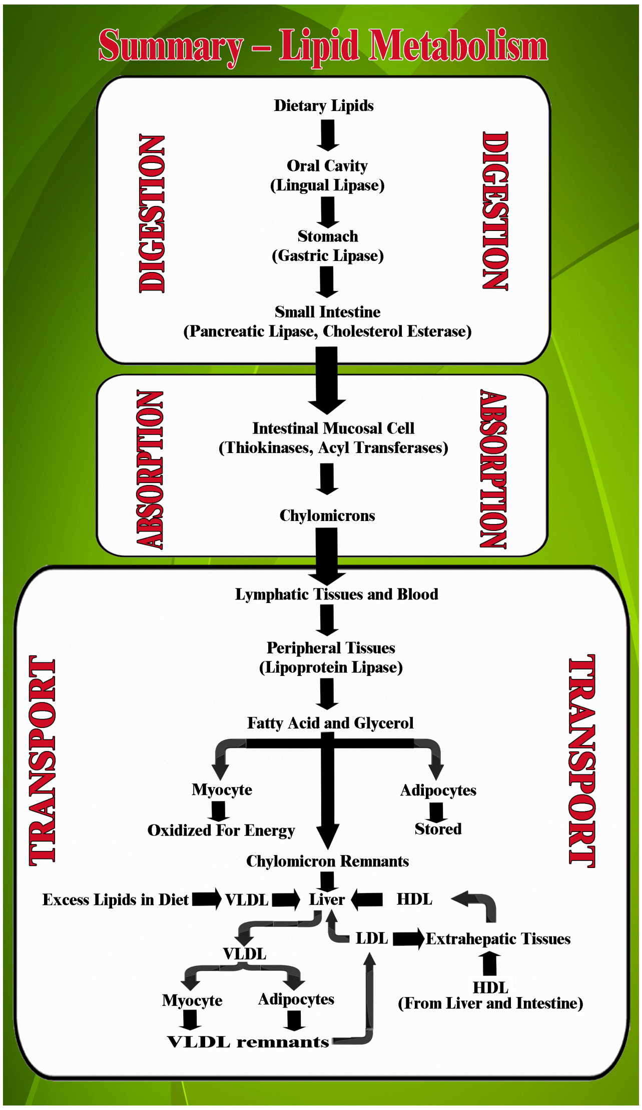

Figure 2. Various Steps in Lipid Metabolism.

It also needs to be emphasized that cellular uptake and regulation of cholesterol is mediated by lipoprotein receptors especially located on the surface of the cells. For transport in plasma, TGL and cholesterol are packaged into lipoproteins, which are then taken up and degraded by cells to fulfill the demands for cellular functions [11,59].

Thus, since lipids play a substantial role in maintaining cellular integrity, it is not surprising that altered lipoprotein patterns also have been associated with malignancies. Patients suffering from OC exhibit altered levels of TC, TGL, HDL-C, LDL-C and VLDL-C [59]. Also, altered lipid profile patterns are observed in other malignancies such as hematological neoplasms, breast cancer, ovarian cancer, etc. [60-63]. Herein we discuss about the alterations in each of the lipid profile parameters specifically and also try to explain the hypothesis behind altered levels of each parameter (*Table 1*).

Total Cholesterol

Low levels of cholesterol in the proliferating tissues and in blood compartments could be due to the ongoing process of oncogenesis. The question arises whether hypolipidemia is a predisposing factor or result of cancer. However, studies have reported that hypolipidemia may result due to the direct lipid-lowering effect of tumor cells or some secondary malfunction of the lipid metabolism or secondary to antioxidant vitamins [12,38,55,59,64-67]. Cholesterol is an essential constituent of lipoprotein fractions like HDL-C, LDL-C and VLDL-C. Seventy-five percent of the plasma cholesterol is transported in the form of LDL-C. Body cells sequester cholesterol from the LDL-C fraction of lipoproteins. LDL receptors are necessary for metabolizing circulating LDLC levels and nearly 80% of the plasma LDLC is cleared by LDL receptors [11,13,59,68]. High activity of LDL receptors attributes for lowering the serum cholesterol levels [11,13,59,69]. Studies have shown a highly significant reduction in the levels of TC in the oral cancer group as compared with the controls thus supporting the hypothesis postulated above [59].

Parameter	Comparison	Result	Inference
TC	Oral cancer group vs. control group	Statistically significant reduction	Low levels could be due to: • ongoing process of oncogenesis or • high activity of LDL receptors
TGL	Oral cancer group vs. control group	Variable results: • Statistically significant reduction • Statistically significant elevation • Statistically non-significant difference	Reduced levels observed can be due to: • increased lipid utilization due to new membrane formation • lipid peroxidation of cell membrane because of tobacco carcinogens
HDLC	Oral cancer group vs. control group	Statistically significant reduction	Diminished levels can be due to: • consequence of disease that is mediated by utilization of cholesterol for membrane biogenesis of the proliferating malignant cells
LDLC	Oral cancer group vs. control group	Stastically non-significant difference	LDL cholesterol levels per se does not cause cancer
VLDLC	Oral cancer group vs. control group	Stastically non-significant difference	VLDL cholesterol levels per se does not cause cancer
Histopatholo-gical Grading	Between the three histopatholo-gical grades of cancer	Stastically non-significant difference	Lipid levels are independent of grade of oral cancer
Tobacco Abuse	Oral cancer group NHT and WHT vs. control group NHT and WHT	Statistically non- significant difference in their levels	Role of tobacco may not have a direct and overall significant association with serum lipid levels
	Oral cancer group WHT vs. Control group WHT	Significantly reduced TC, HDLC and TGL in Oral cancer group WHT; Statistically non- significant difference in LDLC and VLDLC	Reduced levels may be because of underlying disease process and not because of tobacco habit

TC: Total Cholesterol; **TGL:** Triglycerides; **HDLC:** High-density lipoprotein-cholesterol; **LDLC:** Low-density lipoprotein-cholesterol; **VLDLC:** Very-density lipoprotein-cholesterol; **NHT:** Subjects with no habit of tobacco abuse; **WHT:** Subjects with habit of tobacco abuse

Triglycerides

As far as TGL levels in cancer patients are concerned, there have been conflicting reports, with some of the studies reporting significant reduction in TGL levels in cancer patients as compared with the controls [11,59,70]. However, others have found a non-significant difference in serum TGL between controls and patients [11,53]. Furthermore, still others have observed elevated TGL levels in cancer patients [8,11,71].

The reduced levels of TGLs observed can be explained on the basis that some decrease will be there when there is increased utilization of lipid particles due to new membrane formation during the process of carcinogenesis and also due to lipid peroxidation of cell membrane because of tobacco carcinogens. Although they are not the major part of cell membrane as the cholesterol, they constitute a part of the cell membrane up to some extent. So, it is suggested that both of these factors can affect the total plasma triglycerides levels.

High density lipoprotein cholesterol

HDL-C levels may also serve as a useful indicator, reflecting the initial changes occurring in neoplastic conditions [13] since drastic reduction in levels of HDLC have been observed in numerous reports [8,11,12,54,59,70,72]. This makes us to believe that low HDLC is an additional predictor of cancer and it might be a consequence of disease that is mediated by utilization of cholesterol for membrane biogenesis of the proliferating malignant cells [11,59,70].

Low density lipoprotein cholesterol and very low density lipoprotein cholesterol

In studies conducted by Singh et al. and Chawda et al. serum LDLC and VLDLC levels did not reveal any significant difference between the cancer and control groups [59,70]. It seems, therefore, that low LDL cholesterol levels per se does not cause cancer [73].

Correlation of lipid profile with histopthological grading

Histopathologically, the oral cancer group is graded as well-differentiated, moderately differentiated or poorly differentiated squamous cell carcinoma. Logically speaking the levels of lipid profile parameters should reduce consistently as the grade of OC increases but on the contrary, on comparison of all the lipid levels between the three different groups of oral cancer patients, it has been observed by Lohe et al., Chawda et al and Singh et al. that there was no statistically significant difference found between the groups [12,59,70].

Correlation of lipid profile with tobacco abuse

Tobacco consumption in different forms is highly prevalent in the society. Tobacco contains many carcinogens like nicotine and nitrosamines which are believed to induce generation of free radicals and reactive oxygen species, which are responsible for high rate of oxidation/peroxidation of polyunsaturated fatty acids, the important components of cell membranes. This peroxidation further releases peroxide radicals. These free radicals affect essential constituents of cell membrane resulting in tissue injury, thus damaging the cellular structural blocks like lipids, proteins, DNA, etc., and thus might be involved in carcinogenesis/tumorigenesis [11,12,74].

In the studies when the mean serum TC, HDLC, LDLC, VLDLC and TGL levels between oral cancer group with no habit of tobacco consumption and with habit of tobacco consumption and control group with no habit of tobacco consumption and with habit of tobacco consumption were compared, there was no statistically significant difference in their levels. But, when the serum lipid levels of tobacco consuming subjects in the oral cancer group were compared with the serum lipid profile levels of the tobacco consuming control group to eliminate any bias because of tobacco habit, significant lower levels of mean serum TC, HDLC and TGL were found in the tobacco consuming group of oral cancer as compared with the tobacco consuming group of control subjects. Mean serum LDLC and VLDLC levels did not reveal any significant difference among the two groups. These findings imply that lower lipid levels may be mainly because of the basic underlying disease process and not because of tobacco habit. This suggests that although the role of tobacco has been established as an etiological factor for oral cancer, it may not have a direct and overall significant association with serum lipid levels [12,59].

Conclusion

To conclude, in the present review we have attempted to summarize the basics of lipids and have thrown a light on the various possible associations between the serum lipid profile and OC. This review supports the evidence of an inverse relationship between serum lipid profile and OC. Additionally, it supports the contention that there is no statistical significance of mean serum lipid profile levels between histopathological grades of OC. Moreover, lipid profile has no direct and overall significance associated with tobacco habit. In the light of the observations made in this review paper it needs to be emphasized that the need of the hour is to understand the underlying mechanisms of regulation of plasma cholesterol concentrations in cancer, and this can be realized by in-depth study of alterations in serum lipid profile patterns in patients with OC.

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