ABSTRACT

INTRODUCTION

Cholesterol at either higher or lower level can be troublesome. Health issues related to higher than normal levels have received much public attention because of their relationship to incidence of heart disease, whereas implications of decreased cholesterol levels remain unclear. Lipids are major cell membrane components essential for various biological functions including cell growth and division of normal and malignant tissues. Usefulness of variations in tissue/blood cholesterol levels in diagnosis and treatment of various diseases has been studied by several workers. Although, its prime role in pathogenesis of coronary heart disease has been consistently found, researchers have reported association of plasma/serum lipids and lipoproteins with different cancers. The alterations in the circulatory cholesterol levels have been found to be associated with etiology of breast cancer and colorectal cancer. However, only a few reports are available on plasma lipid profile in patients with premalignant and malignant lesions of Head & Neck region.

BACKGROUND: The changes in lipid profile have long been associated with cancer. Recent advances in the field of biologic science have sparked new interest in the areas of identifying cancer biomarkers in the bodily fluids.

AIMS: The present study evaluated alterations in plasma lipid profile in patients with premalignant and malignant lesions of Head & Neck region.

MATERIAL AND METHODS: This clinical study was conducted in our institution for 2 years. Total of 100 patients, 50 with PM & 50 with M lesions were randomly selected from out-patient visiting the Department of ENT, Head & Neck Oncology, Oral Medicine & Radiology. Plasma lipids: (i) Total cholesterol (ii) LDL cholesterol (iii) HDL cholesterol (iv) VLDL cholesterol and (v) triglycerides analysed.

STATISTICAL ANALYSIS: Student’s t-test was performed to compare mean values of the parameters.

RESULTS: Serum lipids were in normal range in PM and M group and no statistical significant difference between P values when compared.

Epidemiology: There are more than 40,000 new cases of head and neck cancer every year in the United States, and 500,000 worldwide, predominantly consisting of squamous cell carcinoma of the upper aerodigestive tract. The mechanisms underlying carcinogenesis in the head and neck are similar to those mechanisms and principles found in other solid tumors. It is generally accepted that cancer arises from the progressive accumulation of genetic alterations that lead to a selection of a clonal population of transformed cells. In an attempt to classify and understand the biology of sporadic and hereditary retinoblastoma, Knudson first put forth his model of the “two-hit” hypothesis in 1971. He described a model in which two copies of the parental inherited Rb gene were inactivated either by mutation or by loss of chromosomal material, leading to development of hereditary or sporadic retinoblastoma. A model of tumor progression was synthesized by Fearon and Vogelstein into the following three basic tenets:

1. Cancer arises as the result of inactivation of tumor suppressor genes (TSGs) or activation of proto-oncogenes.
2. There is a defined order of genetic events that leads to development of a malignant phenotype.
3. Variations in the order of events can occur, however, and it is ultimately the net accumulation of genetic events that determines the phenotypic expression of malignancy.

Slaughter and colleagues’ first coined the term field cancerization in a histologic study examining the epithelium surrounding invasive cancers. They recognized there were histopathologic changes in the epithelia surrounding invasive oral tumors and...
reported an increased incidence of second primary tumors, usually close to the initial tumor. Other investigators subsequently confirmed a higher incidence of second primary tumors in the upper aerodigestive tract in those patients with initial head and neck primary tumors. The breadth of possible genetic alterations previously discussed as leading to a phenotypic expression of malignancy has grown, although the end targets of genetic alterations almost always involve inactivation of TSGs, activation of proto-oncogenes, or both. TSGs are those genes that are normally present in cells and whose function is to regulate and repress cellular functions that, when left unchecked, would lead to expression of a cancer phenotype. Proto-oncogenes are those genes that, when altered either by aberrant, constitutive activation or DNA copy number amplification, result in inappropriate overexpression or increased activity that results in expression of a malignant phenotype.

Alexopoulos et al have found non-significant difference in serum triglycerides between controls and patients. While others have observed elevated triglycerides levels in cancer patients. Lipid peroxidation is an essential biochemical process that involves the oxidation of polyunsaturated fatty acids, the important components of cell membranes.

Animal studies have shown that nicotine, a known tobacco carcinogen, affects activity of enzymes responsible for lipid metabolism. It is also reported that LDL uptake and cholesterol biosynthesis were decreased in the liver of tumor bearing animals. Further, exposure to tobacco carcinogens hampers antioxidant defense, leading to accelerated lipid peroxidation.

AIMS AND OBJECTIVES
1. To estimate the serum lipid levels in patients with premalignant and malignant lesions & head and neck region.
2. To compare the serum lipid levels of patients with premalignant and malignant lesions of head and neck region with serum lipid levels of healthy individuals.

MATERIALS AND METHODS: The present prospective type of clinical study was conducted in our institution for 2 years. A total of 100 patients, 50 patients with premalignant lesions & 50 patients with malignant lesions were randomly selected from out-patients visiting the Department of ENT, Head & Neck Oncology, Oral Medicine & Radiology.

Inclusion criteria
- Patients with clinically evident oral premalignant lesions.
- Patients with histopathologically confirmed head and neck malignancy.
- Patients of 20 years of age and above.

Exclusion criteria
- Patients with metabolic disorders.
- Patients older than 75 years.
- Patients with obesity.
- Patients with OSMF.
- Patients with thyroid gland malignancy.
- Patients on cytotoxic drugs or radiotherapy for oral cancer.

RESULTS AND OBSERVATIONS
A total of 50 patients with premalignant and 50 with malignant lesions of head and neck region who fulfilled the inclusion criteria were evaluated after a detailed history, general physical examination and complete E.N.T examination after randomly selecting them from out-patients visiting the Department of ENT, Head & Neck Oncology, Oral Medicine & Radiology Department and divided into two groups. Informed consent was obtained from all study participants and/or their caregivers.

2. Group M: with malignant lesions of head and neck

The following observations were noted:

1. Age distribution.
2. Sex distribution
3. Site of lesion
4. HPE
It was observed that 37% of patients had oral leukoplakia followed by 13% with oral erythroplakia and 3% with leukoplakia of vocal cords in PM group and 43% had squamous cell carcinoma in the M group.

### 5. Tumor size in M group

![Tumor size in M group](image)

It was observed that maximum number 38% were in T3.

### 6. Histological grade in M group

![Histological grade in M group](image)

It was observed that maximum 42% patients had moderately differentiated cancers.

### 7. Nodal status in M group

It was observed that 72% had positive node involvement in M group.

![Nodal status in M group](image)

### 8. Distribution of serum lipid profile in both groups.

![Serum Lipid distribution](image)

It was observed that there was no statistical significant difference between P values when compared with both PM and M group.

### DISCUSSION

Our study group consisted predominantly of males in both premalignant PM group (96%) and malignant M group (82%). It was observed that the maximum number of patients belonged to age group 41-50 years in PM group and 51-60 years in M group.

Lipids are major cell membrane components and are essential for all animal life. It is primarily synthesized from simpler substances within the body. They play an important role during cell growth & division and in activities of enzymes. It is synthesized in many tissues from acetyl-CoA and is ultimately eliminated from the body in the bile as cholesterol or bile salts.

Since cholesterol is insoluble in blood, it is transported in the circulatory system within lipoproteins. Lipoproteins are clusters of proteins and lipids all tangled together to carry lipids in blood. There are several types of lipoproteins within blood called chylomicrons, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Higher densities of lipoproteins are due to more amount of cholesterol as compared to protein moiety. HDL is associated with carrying cholesterol out of the blood system and LDL transports 75% of plasma cholesterol. Chylomicrons are lipoprotein transporters in the intestine. VLDL molecules are produced by the liver and contain excess triacylglycerol and cholesterol that is not required by the liver for synthesis of bile acids. LDL molecules are the major carriers of cholesterol in the blood. HDL particles are thought to transport cholesterol back to the liver for excretion or to other tissues that use cholesterol to synthesize hormones. Thus, higher levels of HDL are essential for maintenance of healthy tissue.

The different lipoproteins contain apolipoproteins, which serve as ligands for specific receptors on cell membranes. Cellular uptake and regulation of cholesterol is mediated by these receptors located on the cell surface. In plasma, triglycerides and cholesterol are packaged into lipoproteins. These lipoproteins are then taken up and degraded by the cells which are needed for functioning of cells. It is believed that levels of lipids vary with malignancy. Lipids are being utilized in maintaining the integrity of cells in the malignant tissue.

Raised levels of lipids have strongly been associated with pathogenesis of coronary heart disease. Hypolipidemia often goes unnoticed and often physicians are unaware of the causes and consequences of hypolipidemia. Lower levels of lipids have been reported to be associated with septicaemia, in critically ill patients and at times with the existing malignancy. It may not play a role in carcinogenesis but a lower level of lipids may indicate rapidly dividing cells in malignancy. This can serve as a marker in early neoplastic changes, in follow up cases and as a prognostic indicator of disease. The mechanism for the association of cancer with cholesterol remains controversial. The exact mechanism of its role in carcinogenesis is not clearly defined. More lipids are required for synthesis of cell membrane and the demand is met from degradation of lipoproteins in circulation. Genes and hormones also interact to regulate the plasma cholesterol levels.

There are the three main competing hypotheses to explain the inverse association between cholesterol concentrations and the incidence of 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 the 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 increased membrane permeability to cholesterol precursors and trans fatty acids. However, fatty acid studies have reported that hypolipidemia may result because of the direct lipid lowering effect of tumor cells or other secondary malfunction of the lipid metabolism or secondary to antioxidant vitamins. It is widely demonstrated that oral cancer interfaces significantly on food intake as well as on lipid ingestion and absorption. Therefore, it can be expected that oral cancer induces low serum levels of lipids, but the other factors, such as genes and hormones, also interact to regulate the plasma cholesterol levels in man. These mechanisms can be understood through lipoprotein transport system. Crucial components of this system are lipoprotein receptors in the liver and extra hepatic tissues that mediate the uptake and degradation of cholesterol-carrying lipoproteins. Lipoproteins are degraded as they deliver their cholesterol to tissues, whereas the cholesterol survives eventually to be excreted from the tissues bound to new lipoprotein carriers. Exit of cholesterol from the body occurs only when the sterol is transported to the liver for excretion into bile. Because of the continuous cycling of cholesterol into and out of the blood stream, the plasma cholesterol concentration is not a simple additive function of dietary cholesterol intake and endogenous cholesterol synthesis. Rather, it reflects the rate of synthesis of the cholesterol carrying lipoproteins and the efficiency of the receptor mechanisms that determine their catabolism. Thus, the cholesterol homeostasis in healthy subjects depends on the presence and function of specific receptors on the cellular surface. These receptors normally control the degradation of LDL. The major cholesterol transport protein in human plasma. In the neoplastic disease, an increased LDL activity in tumor cell may produce hypcholesterolemia. The results and observations of the serum lipid profile assay in the present study showed that there was no decrease in TC, LDL and triglyceride in malignant group as compared with premalignant group. In some malignant diseases, blood cholesterol undergoes early and significant changes. Low levels of cholesterol in the proliferating tissues and in blood compartments could be due to the process of carcinogenesis. People diagnosed with cancer were noted to have low cholesterol levels, but it was not clear whether this was a cause or an effect of cancer. Return of serum cholesterol levels to normal in responding patients suggested that tumor burden was inversely related to cholesterol levels rather than the propensity of individuals with lowered cholesterol to develop cancer. In the present study, a significant decrease was observed in serum HDL in oral cancer and OPC patients. The low HDL is an additional predictor of cancer and it might be a consequence of disease that is mediated by utilization of cholesterol for membrane biogenesis. The excessive use of tobacco products has been associated with various lesions in the oral cavity. It is believed that tobacco carcinogens induce generation of free radicals and reactive oxygen species, which are responsible for high rate of oxidation peroxidation of polyunsaturated fatty acids. In our study it was observed that the serum lipids were in normal range in both PM and M group and there was no statistical significant difference between P values when compared with both PM and M group.

CONCLUSION AND SUMMARY:

The conclusions drawn from the study were as follows:

1. The mean ± standard deviation of age was 44.3±9.81 and 58.1±10.68 respectively in PM and M group.
2. It was observed that the maximum number of patients belonged to age group 41-50 years in PM group and 51-60 years in M group.
3. It was observed that in PM group 96% were males and 4% were females and in M group 82% were males and 18% females.
4. It was observed that 47% of the patients had lesion in oral cavity in PM group and 19% in M group. Both larynx and pharynx were involved in 12% of cases.
5. It was observed that in PM group, 37% of patients had oral leukoplakia followed by 13% with oral erythroplakia and 3% with leukoplakia of vocal cords and 43% in M group had squamous cell carcinoma.
6. It was observed that maximum number of 38% showed T3 stage.
7. It was observed that maximum 42% patients had moderately differentiated cancers.

8. It was observed that 72% had positive node involvement in M group.
9. It was observed that the serum lipids were in normal range in both PM and M group and there was no statistical significant difference between P values when compared with both PM and M group.

Technology is poised to play an active role in the diagnosis of patients with premalignant and malignant lesions. The advanced techniques such as FISH are now used at a handful of research centres. Until more laboratories acquire needed molecular technologies, routine histopathologic examination is likely to remain the standard for detection of most patients. With earlier detection, treatment is less complicated, the cosmetic and functional results are better and survival improved. Hence, the importance of identifying cancer biomarkers in bodily fluids is crucial and can be a huge milestone in the history of mankind.

References:

16. Gilbert MS, Ginsberg H, Fagenstein R, Brown WV. Characterization of scavenger receptors in human monocytes: local actions of cholesteryl ester transporter for detection of most patients. With earlier detection, treatment is less complicated, the cosmetic and functional results are better and survival improved. Hence, the importance of identifying cancer biomarkers in bodily fluids is crucial and can be a huge milestone in the history of mankind.