Lipid Profile in Leukoplakia and Oral Cancer

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Abstract

Background and objective: Abnormal lipid profiles have been associated with cancer as lipids play an important role in biological functions like cell growth and maintenance of cell integrity. Various studies in the past have shown an inverse relationship between plasma lipid levels and malignancy of blood, gastrointestinal tract, lungs, brain and other head and neck carcinomas. The present study was done to evaluate the plasma lipid profile in patients with untreated oral cancer, patients with leukoplakia as compared with age and sex matched controls.

Method: This study included 90 subjects among which 30 patients with oral cancer, 30 patients with leukoplakia and 30 age and sex matched subjects as controls. Plasma lipids including Total cholesterol, High density lipoprotein, Low density lipoprotein, Very low density lipoprotein, and Serum triglycerides were evaluated by enzymatic methods.

Results: A decrease in total cholesterol and HDL was observed in cancer patients as well as leukoplakia (p-value of 0.195 and 0.219 respectively) as compared with controls. A significantly decreased LDL levels was observed in cancer patients (p<0.001*) as compared with patients with leukoplakia and controls. VLDL and triglycerides levels were higher in cancer and leukoplakia patients as compared with controls (p<0.011* and 0.007** respectively). TC, HDL and LDL were lower in tobacco habituates than nonhabituates. Our data also showed the evidence of inverse relationship between plasma lipid levels in oral cancer and leukoplakia.

Conclusion: From our result, it was evident that an inverse relationship between plasma lipid levels and oral cancer as well as leukoplakia as seen in other malignancies. The lower levels of plasma cholesterol and other lipid constituents might be due to their increased utilization by the neoplastic cells for new membrane biogenesis. These findings strongly warrant an indepth
study on alterations in plasma lipid profile in oral cancer and premalignant disorders.

**Keywords:** Lipids, Cholesterol, Triglycerides, Lipoproteins, Oral cancer, Leukoplakia.

**Introduction**

Even through various advances and sophisticated diagnostic and treatment modalities in the field of medicine, it continues to be haunted and humiliated by one word – Cancer. It still remains an enigma despite intensive effort throughout the world and mankind achieving great strides in this field. Since decades, various advances in the field of cancer was achieved through immune-histochemistry, tumor associated enzymes, hormones, proteins, vitamins and identification of chemical substances in the blood known as tumor markers. These contribute to the diagnosis and in some instances are useful in determining the effectiveness of therapy. The international agency for research of cancer (IARC) has shown that the malignant neoplasms of oral cavity, pharynx and salivary glands are responsible for an estimated 3.9% of total new cases of cancer worldwide. Among these approximately 65,000 cases are reports from India. Oral Squamous Cell Carcinoma generally arises in middle aged and older people, with a male to female ratio greater than 2:1. This ratio is changing because of increased incidence of tobacco and alcohol use among women. In many regions of India, oral cancer ranked first among all cancers in males and third most common cancer among females. Various studies have reported that 80% of the oral cancers result from the progression of precancerous lesions like erythroplakia and leukoplakia. Moreover, 16% to 62% of the oral cancers are associated with leukoplakia at the time of diagnosis. The malignant transformation rate of oral leukoplakia is found to vary from 6.6% - 36%. The prevalence of leukoplakia varies from 0.2%-4.9%. Numerous studies have reported altered lipid profile in various malignancies including that of head and neck cancers. Increased mortality rate was observed with lower plasma lipid profile in cancer subjects, while rise in their level during the treatment. Similar correlation between the tobacco habituates and lipid profile have also been noted. Even though the lipid profile have been evaluated in various malignancies no much studies exists comparing it in oral cancer. Hence in our present study, evaluation of plasma lipid profile in oral cancer and its correlation with leukoplakia compared with the age and sex matched controls, were undertaken.

**Materials and Method**

Five ml of blood was drawn from the individuals and serum was separated by centrifugation. The Plasma lipid profiles were estimated through enzymatic methods. The parameters considered were total cholesterol (TC), High density lipoprotein (HDL), Low density lipoprotein (LDL), Very low density lipoprotein (VLDL) and triglycerides. Reagents kits available for estimation of the HDL, Cholesterol and triglycerides were used. Once these reagents were reconstituted and brought to the room temperature, 1ml was taken in different test tubes and 10μl of sample was pipetted and mixed well. This was incubated for 5 mins at 37°C, and the values were recorded at various wavelength; 500nm for total cholesterol, 600/700nm for HDL, and 546nm wavelength for triglycerides. The VLDL and LDL values were calculated using the formula: Triglyceride / 5 = VLDL and TC – HDL- VLDL = LDL

Chi-square and Fisher Exact test were used to test the significant proportion of abnormal lipid parameters between three groups.
Results

Group I had 30 oral cancer patients of equal gender predilection with a deleterious habit of chewing and smoking tobacco. However, there was a wide age distribution ranging from 21– 80 years. The clinical staging of these patients accordingly were 3.3% in stage I and II, 43.3% in stage III and 50% in stage IV. The age distribution in group II with leukoplakic lesion was also between 21-80 years, of which 17 were males and 13 were females with chewing tobacco and smoking being the common deleterious oral habit among them. In group III, 30 age matched subjects were selected as control with equal number of males and females. The subjects in this group did not have any deleterious oral habits.

The plasma lipid levels were estimated in all the 3 groups and the arithmetic mean along with standard deviation of all the parameters was calculated. The lipid parameters included were Total cholesterol, HDL, LDL, VLDL, Triglycerides, and ratios of TC/HDL, LDL/HDL. The abnormal lipid parameters according to the number of patients affected in all the three groups were calculated. (Table 1, graph 1)

The changes in the total cholesterol and VLDL level in all the three groups was not statistically significance. Statistically significant changes in HDL levels were seen among the three study group with a p value of 0.0067** and p value of <0.0001** was seen in the LDL value.

Table 1: Comparison of levels of Lipid parameters between three groups

Results are presented in Mean ± SD (Min-Max)

<table>
<thead>
<tr>
<th>Lipid Parameters</th>
<th>Group I (n=30)</th>
<th>Group II (n=30)</th>
<th>Group III (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (TC) (mg/dl)</td>
<td>193.87±48.35 (138-365)</td>
<td>185.00±34.22 (120-279)</td>
<td>201.70±16.34 (181-235)</td>
<td>0.195</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>39.50±5.82 (26-35)</td>
<td>38.83±5.08 (28-50)</td>
<td>41.00±3.48 (37-48)</td>
<td>0.0067**</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>116.11±35.54</td>
<td>119.93±29.54 (56-162)</td>
<td>142.13±13.14 (118-168)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>151.30±78.12 (71-430)</td>
<td>159.37±12.64 (64-657)</td>
<td>93.40±34.59 (25-189)</td>
<td>0.007**</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>4.92±0.93 (3.23-7.60)</td>
<td>4.77±0.71 (3.24-6.24)</td>
<td>4.92±0.13 (4.69-5.44)</td>
<td>0.642</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>2.96±0.82 (0.75-4.79)</td>
<td>3.12±0.72 (1.51-4.11)</td>
<td>3.47±0.12 (3.03-3.62)</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

Graph 1: Comparison of abnormal Lipid parameters between three groups

Discussion

The lipids are a heterogenous group of compounds known by their physical properties rather than by chemical activities. They are an efficient source of energy, a thermal insulator, and form important cellular constituents along with proteins, in cell membrane and mitochondria within the cytoplasm. Cholesterol and triglycerides being important lipid constituents of cells, are essential for various physiological functions. Cholesterol is essential for maintenance of structure and functional integrity of all biological membranes and for stabilization of DNA helix. The major functions of the plasma lipoproteins are transport of triglycerides and cholesterol from sites of synthesis to sites of storage, energy use or metabolism. The VLDL transports the endogenous synthesized triglycerides, LDL are the biologic vehicle to provide cholesterol to the peripheral tissues, HDL transports...
cholesterol from peripheral tissues to liver for degradation.\textsuperscript{10}

Cholesterol depletion from plasma membrane results in anoikis like apoptosis and this type of cell death is significant in prostate and breast cancer cell lines that possess higher levels of membrane cholesterol. It was observed that malignant cells have elevated rates of mevalonate synthesis a precursor of cholesterol which has been reported to promote tumor growth.\textsuperscript{11}

Lipid metabolism of tumors may be different from that of normal tissue but the relationship between tumor genesis and changes in the amounts or composition of circulating plasma lipids is unclear. Several studies have reported differences in total plasma lipid levels and also in relative amounts of plasma lipoproteins between untreated cancer patients and healthy subjects.\textsuperscript{12}

Low levels of cholesterol in the proliferating tissue and in blood compartments could be due to the process of carcinogenesis. Plasma cholesterol upto 75\% is transported in the form of LDL. LDL receptors are necessary for metabolizing 80\% of circulating LDL levels. This amounts to a reduction in the plasma cholesterol levels.\textsuperscript{8} The deficient or defective LDL receptor remove plasma LDL at a lower rate and hence elevated levels of LDL are seen in plasma. The decrease in HDL might be a consequence of disease that is mediated by utilization of cholesterol for membrane biogenesis.\textsuperscript{8}

Several retrospective and prospective studies in the past have shown an inverse relation between serum cholesterol levels and cancer incidence.\textsuperscript{13} However, no causative relation has been reported till date. Further, few studies have reports of hypocholesterolemia as a result rather than the cause of malignancy.\textsuperscript{13,14} Irrespective of various hypothesis, hypocholesterolemia and associating lipoprotein disorder was found to be a constant findings in the untreated malignant patients.\textsuperscript{13}

Hypocholesterolemia has often been reported at diagnosis stage in patients with various forms of malignancies. Halton et al have shown an inverse relationship between cholesterol level and disease stage and mortality in various malignancies of head and neck, blood, prostate, brain, GIT, Colorectal cancer and lung cancers.\textsuperscript{15}

The concept of a two-step process of cancer development in the oral mucosa, \textit{i.e.}, the initial presence of a precursor premalignant lesion subsequently developing into oral cancer, is well established. Oral leukoplakia is one of the best-known premalignant lesion in the oral cavity that has the highest rate of malignant transformation.\textsuperscript{2} Hence, the present study was conducted to observe the relationship between lipid profile and oral cancer.

The total cholesterol level was slightly lower in oral cancer and leukoplakia patients than that of controls with a \textit{p} value of 0.195, which was in accordance with various studies on malignancies of head and neck, and blood\textsuperscript{7,13,15} However in malignancy of breast cancer an increase in total cholesterol level was reported.\textsuperscript{41} Further Halton et al and Manolio et al in their studies have reported lower cholesterol levels in widespread disease than local tumors with a relatively high risk of mortality.\textsuperscript{15,16} The lower level of TC was attributed to increased utilization by tumor cells.\textsuperscript{14,16}

In the present study a slightly lower levels were observed in plasma HDL cholesterol in cancer and leukoplakia patients with a \textit{p} value of 0.219. The range of HDL values in oral cancer and leukoplakia was 26-35 mg/dl and 28-50 mg/dl respectively which was lower than that of controls (37-48 mg/dl). This finding was in accordance with previous reports, that low HDL is an additional predictor of cancer.\textsuperscript{7,8,13,15,17,25,26,28,29,30} Patel et al stated that the lower HDL level may be a consequence of disease that

is mediated by utilization of cholesterol for membrane biogenesis.\textsuperscript{13,15,18}

A significantly lower level of LDL was observed in the present study in cancer patients than that of controls with a p value of 0.001**. This is contradictory to the study of Patel et al on head and neck malignancies who reported elevated levels.\textsuperscript{8} Lower level of cholesterol in blood malignancies.\textsuperscript{7,15} Budd et al stated that the levels of LDL appears to be related to the activity of the disease, rather than the cause of it. However, several mechanisms might be possible.\textsuperscript{7} The increased LDL catabolism by mature monocytic phagocytes might be the basis for the reduced plasma LDL concentration in patients with acute myelogenous leukemia (AML). It was suggested that reduced LDL cholesterol concentration in plasma with AML would be the presence of de-repressed neoplastic cells with increased utilization of cholesterol for membrane synthesis.\textsuperscript{7}

A significantly higher VLDL levels was observed in oral cancer patients in the present study with a p value of 0.11* which was observed by Chang et al only in the breast cancer patients \textsuperscript{25} and was not inferred by malignancies of head and neck by Patel et al.\textsuperscript{8}

A significantly higher triglyceride levels was observed in cancer patients in the present study which was a similar findings as that of Naik et al,\textsuperscript{13} Halton et al 1998 in AML patients\textsuperscript{57}, Raste et al 2000 in various cancer patients\textsuperscript{15,17,19} and Mydlo JH et al 2001 in prostate cancer patients.\textsuperscript{13}

Comparing the lipid profiles with and without the habit of tobacco, the total cholesterol, HDL, LDL showed lower levels among the subjects with the habit of tobacco than the controls suggesting that tobacco habituates have a lower cholesterol levels which was in accordance with various other studies\textsuperscript{27}. Halton et al have shown an inverse association between smoking and HDL cholesterol, (p<0.001). A strong association was also found between smoking and LDL-cholesterol (p<0.01). Triglycerides and VLDL-cholesterol showed a weak association with smoking in this study.\textsuperscript{20,27} Abiaka et al 2001 showed a significantly decreased TC in smokers with a P value of <0.0001.\textsuperscript{21} Rithesh et al 2006 also reported an 2.5 times higher the risk of hypocholesterolemia in smokeless tobacco users than controls and in Indian population. Smokeless tobacco users had lower HDL and higher triglyceride level than that of nonusers.\textsuperscript{22} d Alcoholics demonstrated an 8% decrease in the LDL levels.\textsuperscript{23}

Various authors have suggested that the reduction in the cholesterol value was due to an effect of cancer on cholesterolemia and onset of malignancy was not due to low cholesterol levels.\textsuperscript{24,28,29} But it has also been suggested that the lipid profiles could be used as a prognostic indicator to assess the outcome of treatment as TC and LDL levels have shown an increase in its baseline value after treatment.\textsuperscript{7}

\textbf{Conclusion}

In our present study a slight decreased TC and HDL levels were noted in oral cancer patients as compared with controls. Stastically significant changes were noted in LDL levels among the oral cancer patients. A significantly decrease in LDL levels of oral cancer patients compared to that of controls and leukoplakia patients. VLDL and triglyceride values showed significantly increase in oral cancer compared to controls. Comparing the lipid parameters between tobacco users with nonusers, TC, HDL, LDL were significantly decreased and VLDL, triglycerides showed increased levels in tobacco users,. Although an inverse relation between TC, HDL and LDL were observed in the present study in accordance with various other malignancies, a further indepth study would help in assessing the usefulness of lipid profile in oral cancer and leukoplakia.
Reference


