ORIGINAL RESEARCH

Alterations in Serum Lipid Profile in Oral Cancer and Oral Submucous Fibrosis Patients: A Clinicopathological Study.

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Abstract

Introduction: Oral cancer is the sixth most common cancer worldwide. Oral submucous fibrosis (OSMF) is one of the commonest potentially malignant disorders in India. Hypolipidemia can be considered as one of the biochemical markers in early detection of cancer. This study was undertaken to evaluate the role of serum lipids as tumor markers in the diagnosis of oral precancerous lesions and oral cancer.

Aim: To evaluate the alterations in lipid profile in OSMF, OSCC patients and to compare the levels with respect to the clinical staging and histological grading of OSMF.

Methods and Materials:70 patients of OSMF and 60 patients of OSCC diagnosed clinically and histopathologically were included as the study subjects. A group of 70 age and sex matched normal subjects were taken as controls. The serum lipid profile consisting of TC, TGs, HDL, VLDL and LDL were calculated using Roche Cobas III autoanalyzer. Statistical analysis used: one-way ANOVA and Scheffe post hoc was applied.

Results: The serum lipid level was statistically significantly lowered in patients with oral cancer and OSMF when compared with normal control group. All the lipid profile parameters such as TC, TG, HDL, VLDL and LDL progressively reduced as clinical stage progresses and the histological grade advanced.

Conclusion: There is an inverse relationship between serum lipid profile in oral cancer as well as in OSMF. The lower serum lipid status may be considered as a useful biochemical marker for early detection of cancer. The decreased serum lipid profile may be considered as a useful indicator for initial changes occurring in the cells of potentially malignant disorders like OSMF.

Keywords: Serum lipid profile, Oral submucous fibrosis, Oral squamous cell carcinoma, Oral cancer.

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Introduction

Oral cancer is the sixth most common cancer worldwide with a report of 75000–80000 new cases in India annually.[1] Nearly 94% of all oral cancer cases are oral squamous cell carcinomas (OSCCs).[2] It is one of the most common malignancies in India, accounting for 30 to 40% of all cancers. Squamous cell carcinoma of the oral cavity is responsible for considerable morbidity and mortality in India, where 60,000 new cases of oral cancer are reported to occur every year.[3] OSCC is often preceded by oral pre-cancerous lesions and conditions; the common among them are the oral leukoplakia and oral sub-mucous fibrosis (OSMF). These lesions display the metabolic and histological activity similar to cancerous lesions and have potential for malignant transformation. Around 0.3-25% of leukoplakia and 7-12% of oral submucous fibrosis cases will undergo malignant transformation.[4,5] OSMF, an insidious chronic disease, reported mainly in Indians associated with the use of areca nut is a precancerous condition and has a significant tendency to develop oral and oesophageal cancer. It is predominantly seen in Southeast Asia and Indian subcontinent with few cases reported from South Africa, Greece and United Kingdom. The prevalence rate of OSMF in India is about 0.2–0.5%.[6]

The habit of chewing and sniffing areca nut and tobacco in various forms is a known etiologic factor for development of oral precancerous conditions and head and neck cancer.[7] It is believed that these carcinogens induce generation of free

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radicals and reactive oxygen species, which are responsible for high rate of oxidation/ peroxidation of polyunsaturated fatty acids. This peroxidation further releases peroxide radicals. This affects essential constituents of the cell membrane and might be involved in carcinogenesis/tumorigenesis.[8] Accumulation of genetic alterations is the basis for the progression of a normal cell to a cancerous cell.[9] The development of a malignancy requires uncontrolled and excessive proliferation of cells. The newly forming cells would require many basic components well above the normal limits, used in physiological processes. One such component is lipid. They are major cell membrane components essential for various biological functions including cell growth and division of normal and malignant tissues. As the neoplastic disease is related to new growth, there is a greater utilization of lipid, including total cholesterol (TC), lipoproteins and triglycerides (TGs) for new membrane biogenesis. Cells fulfill these requirements either from circulation or from degradation of major lipoprotein fractions such as very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) or high-density lipoprotein (HDL).[10] The efficacy of variations in plasma or serum lipid levels in the diagnosis and treatment of various diseases such as breast cancer, colorectal cancer, heart diseases have been studied by several workers.[6] Hence, the aim of the present study was to evaluate the alteration of serum lipid profile in OSMF and OSCC and to compare and correlate the serum lipid levels in different clinical stages and histological grades of OSMF.

Materials and Methods

The study was conducted at Department of Oral Pathology and Microbiology. The study subjects were selected from those who visited the Outpatient Department of Oral Medicine and Radiology. A study was conducted after obtaining the Institutional Ethical Committee clearance [MIDSR/IEC/837/919/15/2021]. Case proforma including patient's consent was made to record signs, symptoms, detailed history, including habits and extended lipid profile estimation.

The subjects were divided into the following three groups.

Group I consisted of 60 clinically and histopathologically diagnosed cases of OSCC.

Group II consisted of clinically diagnosed and histopathologically proven cases of 70 OSMF. The OSMF cases were staged clinically according to Lai et al.[11] and were graded histopathologically according to Utsunomiya H, et al.[12] Group III (control group) consisted of 70 normal subjects age and sex matched without any pernicious oral habits. Patients with systemic diseases like obesity, uncontrolled diabetes mellitus, thyroid disorder, liver dysfunction, malabsorption syndrome, renal dysfunction and cardiac patients were excluded from the study. Thorough history taking and clinical examination

Table 1: Comparison of serum lipid profile levels in oralsubmucous fibrosis patients, oral squamous cell carcinoma patients and control group patients

Lipid Parameters	Control	Oral submucous fibrosis	Oral squamous cell carcinoma	P value by ANOVA
TC(mg/dL)	180.06	151.67	140.36	0.000*
TG(mg/dL)	141.80	138.04	132.47	0.000*
HDL(mg/dL)	47.10	31.27	30.45	0.000*
LDL(mg/dL)	111.96	88.75	84.51	0.000*
VLDL(mg/dL)	30.07	27.98	25.44	0.014*

Table 2: Comparison of serum lipid profile levels in oralsubmucous fibrosis patients of various clinicalstages

Lipid Parameters	Stage 1	Stage 2	Stage 3	Stage 4	P value by ANOVA
TC(mg/dL)	159.71	154.06	145.99	139.00	0.000*
TG(mg/dL)	144.09	138.08	137.06	135.01	0.000*
HDL(mg/dL)	37.05	32.06	26.98	23.98	0.000*
LDL(mg/dL)	95.08	88.07	84.93	82.00	0.000*
VLDL(mg/dL)	29.07	28.07	22.15	23.72	0.000*

Table 3: Comparison of serum lipid profile levels in different histological grades of oral submucous fibrosis

Lipid Parameters	Grade 1	Grade 2	Grade 3	P value by ANOVA
TC(mg/dL)	158.40	150.54	140.86	0.000*
TG(mg/dL)	139.73	137.39	134.79	0.000*
HDL(mg/dL)	35.89	29.50	25.14	0.000*
LDL(mg/dL)	93.43	86.56	83.56	0.000*
VLDL(mg/dL)	28.70	27.92	23.73	0.000*

were carried out and recorded in a specific proforma. They were recalled on the next day with minimum 12 h of fasting for blood examination for complete lipid profile.

Fasting blood samples were collected in plain vials. Centrifugation was done for about 4–5 min at 2500 rpm and Serum was stored in the refrigerator until analyzed. Serum levels of TC, TG, HDL, VLDL and LDL were calculated by using Roche Cobas III autoanalyzer.

Statistical analysis:

Collected data were analyzed using SPSS 16. Percentages, mean, standard deviation, and one-way ANOVA with Bonferroni correction and Scheffe post hoc at 95% confidence interval was used to analyze and compare the serum lipid profile in control group, OSMF groups and OSCC group. Analysis of variance (ANOVA) was used to assess statistical significance of difference between all the groups of OSMF.

Results

A total of 200 cases included in study in which 70 cases were of control group, 60 cases were of OSCC and 70 were OSMF cases. Of 70 OSMF patients, according to clinical staging, Group A were 24 cases (34%), Group B-18 cases (27%), Group C- 16 cases (22%) and Group D- 12 cases (17%), respectively. The cases were graded histopathologically as early stage 31 cases (44%), intermediate stage -22 cases (31%) and advanced stage-17 cases (24%).

Comparison of serum lipid profile levels in oral submucous fibrosis patients, oral squamous cell carcinoma patients and control group patients

There is a significant difference between the means of normal, OSMF, and oral cancer patients in total cholesterol, triglycerides, high-density cholesterol, low-density cholesterol and very low-density cholesterol. [Table 1]

Comparison of serum lipid profile levels in different clinical stages of oral submucous fibrosis patients

The mean TC, TG, HDL, VLDL and LDL [Table 2] levels showed a progressive decrease as the clinical stage of OSMF advanced with a statistically significant P value of 0.00001, 0.00001, 0.00001, 0.00001 and 0.00001, respectively by using one-way ANOVA test.

Comparison of serum lipid profile levels in various histological grades of oral submucous fibrosis

The mean TC, TG, HDL, VLDL and LDL [Table 3] levels showed a progressive decrease as the histological grade of OSMF advanced with a statistically significant P value of 0.00001, 0.00001, 0.00001, 0.00001 and 0.00001, respectively by using one-way ANOVA test.

Discussion

Cancer of oral cavity is highly challenging and an unresolved problem for the human population as on date, particularly with regard to Indian population. OSMF is a chronic debilitating disease and a premalignant condition of the oral cavity. Oral cancer is the leading cause of morbidity and mortality in India and is most commonly preceded by clinically definable premalignant lesions and conditions. OSMF has been identified as a precancerous condition with the highest rate of malignant transformation, shows a significant tendency to develop cancer amongst potentially malignant disorders.[13] Early detection of these lesions can dramatically improve the treatment outcome and prognosis in such patients. 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.[14]

Cholesterol and triglycerides are imperative lipid components of the cell and are critical in carrying out necessary physiological functions such as maintaining structural and functional cell integrity.[15] It is also involved in the activity of membrane-bound enzymes and is important for stabilization of the DNA helix. Lipoprotein receptors located on the surface of the cells mediate cellular uptake and regulation of cholesterol. TGL and cholesterol are packaged into lipoproteins for transport in plasma which are then taken up and degraded by cells to fulfill the requirement for cellular functions.[16] In cases of malignancy, significant changes in serum cholesterol occur.[15] It is has been recognized that oral cancer significantly interferes with food intake as well as lipid ingestion and absorption. Therefore, patients with oral cancer are expected to have low serum levels of lipids; however, other factors, such as genes and hormones, also intermingle to regulate the plasma cholesterol levels. These mechanisms can be understood through the lipoprotein transport system. Lipoprotein receptors in the liver and extrahepatic tissues are the crucial components of this system that mediate the cellular uptake and degradation of cholesterol carrying lipoproteins. Lipoproteins are degraded because they deliver their cholesterol to tissues, whereas the cholesterol survives eventually to be excreted from the tissues and bind to new lipoprotein carriers. The plasma cholesterol concentration varies due to continuous cycling of cholesterol into and out of the bloodstream.[17]

The relation of high lipid profile and coronary heart disease is well established.[18] Lower blood lipids have been associated with various cancers[19, 20, 21, 22] and head and neck as well as oesophageal cancers.[23,24,25] Furthermore, some investigators have also found relation of low serum cholesterol with increased risk of cancer occurrence and mortality.[26–28] Rose and Shipley[29] reported 66% higher mortality rate because of cancer in cholesterol than in the highest plasma cholesterol. There are three main competing hypotheses to explain the inverse association between cholesterol concentrations and the incidence of cancer. (a) Low cholesterol may be an indicator of cancer process even before cancer manifests clinically. (b) Low cholesterol serves as a marker for some other causal sets of variables, and its association with oral cancer may be secondary even though if it precedes cancer. (c) Low cholesterol levels may precede the development of cancer and may be causally associated with some forms of cancer.[30] Chao et al. reported that the neoplastic cells directly utilize cholesterol for their metabolism resulting in hypolipidemia.[31] Williams et al.[27] 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 carcinogens induced by trans-fatty acids. Reduced cholesterol may be due to increased lipid membrane biogenesis by cancer cells or direct lipid-lowering or altered lipid metabolism or antioxidant activity.

The present study was conducted to evaluate the alteration in serum lipid profile in OSMF and OSCC to compare it with control group. And also, to compare and correlate serum lipid

levels with different clinical staging and histopathological grading of OSMF. The study consisted of 70 subjects of OSMF and 60 subjects of OSCC with the age range of 20–70 years. There was a male predominance of 80% and the patients had an addiction to areca nut, betel quid and tobacco. This is in accordance with previous research.

The results of the present study show that TG, TC, HDL, LDL and VLDL were significantly reduced in the OSCC group when compared with the OSMF group and control group. Similar studies were conducted by Gupta et al,[32] Mehta et al.,[33] Anand, et al[34] Subbulakshmi, et al[35] stating that serum lipid profile had an inverse relationship between plasma lipid levels and OSCC as well as with oral precancerous conditions/lesions. The lower levels of plasma cholesterol and other lipid constituents in patients might be due to their increased utilization during transformation from oral precancer to cancer by neoplastic cells for new membrane biogenesis. These findings were similar to those of the present study ($P < 0.0001$).

Patel et al.[24] Lohe et al.[6] found a significant decrease in TC, HDL, VLDL, and TG but not in LDL in patients with oral squamous cell carcinoma when compared with the control group, whereas in our study significant decrease in LDL levels in OSMF was seen as compared to controls. Since LDL-cholesterol is more susceptible to oxidation in various pathologic conditions, its higher peroxidation occurs during oxidative stress as compared with HDL, which prevents the generation of free radicals responsible for lipid peroxidation.[36]

Garg et al.[37] also conducted a similar study which concluded that there is a decrease in plasma total cholesterol, triglycerides, HDL, LDL, and VLDL in the subjects with the oral precancer and oral cancer as compared to the controls. These results are very similar to our study. This could be because leukoplakia and OSMF is a habit-associated disease with free radical release leading to lipid peroxidation, causing a decrease in the lipid levels.[32,33]

In our study, we compare and correlate the values of serum lipid in different clinical staging and grading of the OSMF. We found the significant decrease in the serum lipid levels as the increase in clinical staging and histopathological grading of the disease. Histopathologically OSMF graded in three groups i.e. Grade 1, Grade 2 and Grade 3, these values were found to decrease progressively as increase in grades of OSMF. It also shows that as the disease progresses i.e. from OSMF stage 1 to stage 3, there is a gradual fall in lipid profile levels. The reduced levels of serum lipid profile in OSMF patients may be a consequence of disease, probably result from increased utilization of lipids by the tumor cells for synthesis of cell membrane. Ajai et al.,[38] Kanthem et al.,[39] conducted a similar study for estimation of serum lipid profile in OSMF patients and compared with control groups, and also in different stages of OSMF. Their study showed significant reduction in serum lipid levels as the disease progressed. They compared mean serum lipid profile in different stages of OSMF, which showed constant decrease in all lipid variables from stage I to stage IV with $P < 0.01$, which is similar to the present study. Tilakaratne et al.[40] reported that areca nut is the main etiological factor for OSMF. Excessive use of areca nut may cause fibrosis due to increased synthesis of collagen and induce the production of free radicals and reactive oxygen species, which are responsible for high rate of oxidation/ peroxidation of polyunsaturated fatty acids which affect essential constituents of cell membrane and might be involved in tumorigenesis.

Kumar et al.,[41] conducted a similar study with histological grades of dysplasia as mild, moderate and severe in oral leukoplakia group. But no correlation could be found between the dysplasia grades in oral leukoplakia and serum lipid profile. Kamath et al[42] studied correlation between histological grades of OSCC, graded into well, moderately, and poorly differentiated carcinomas according to the degree of differentiation. Although, serum TC and HDL decreased with the loss of differentiation, the findings were statistically insignificant. So, no correlation found in histological grades of OSCC patients as well. Also, Lohe et al.[6] in her study correlated the serum lipid profile in different histopathological stages of OSCC found no correlation.

Lipid profile analysis has been done frequently. However not many positive results are noted. This may be due to differences between the studies when various parameters are considered individually. This variability in the values of lipid profiles in OSMF and Oral Cancer may be due to methodological differences. The variability may also arise from multiple reasons such as age, nutritional status, body mass index, exercise habits and the various etiological factors. Follow up results give a broader perspective, need to do follow-up studies in a broader perspective.

Conclusion

- The TC, TG, HDL, VLDL and LDL levels in OSCC patients were reduced as compared with OSMF patients and controls suggesting an inverse relationship between serum lipid profile and cancer. The lower serum lipid status may be considered as a useful biochemical marker for early detection of cancer. The decreased serum lipid profile may be considered as a useful indicator for initial changes occurring in the cells of potentially malignant disorders like OSMF.
- As the TC, TG, HDL, VLDL and LDL levels were decreased as the clinical stage of OSMF advances indicating their role as a reliable biochemical indicator. Also it indicates that hypolipidemia is an early change occurring during carcinogenesis or it may be a cause of cancer.
- All the lipid profile parameters such as TC, TG, HDL, VLDL and LDL were gradually reduced as the histological grade advanced signifying their role as the best prognostic biochemical indicator.

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