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RESEARCH ARTICLE

A Comparative Study of Serum Lipid Profile in Patients with Oral Squamous Cell Carcinoma and Healthy Population in a Tertiary Health Care Centre in North-Western India

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Abstract

Aims and Objectives: The aim of the study was to study serum lipid profile in patients with oral squamous cell carcinoma (OSCC) and to compare their levels with those of healthy population. **Materials and Methods:** This study was done in forty five patients of Oral Squamous Cell Carcinoma and the results were compared with results of forty five age and sex matched healthy controls . Serum obtained from centrifugation of 12 hour fasting blood samples was analyzed on fully automated analyzer Beckman coulter AU-680 for estimating the lipid levels (cholesterol, triglycerides [TGL], and high-density lipids [HDL]) by colorimetric method. Low-density lipid [LDL] values were obtained by calculator. **Results:** The comparison of lipid profile levels between Oral Squamous Cell Carcinoma cases and healthy controls shows statistically significant results for TC, HDL and LDL. **Conclusion:** The change in lipid levels may have an early diagnostic or prognostic role in oral malignant lesions and can be used as a biomarker for OSCC patients.

Keywords: Oral cancer- Oral squamous cell carcinoma- Serum lipid profile- serum lipoprotein

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Introduction

Oral cancer is the sixth most common cancer worldwide [1]. In India, oral cancer incidence is about 3 to 7 times more common compared to developed countries [2]. It is the most common type of cancer in South Asian Countries like India, Sri Lanka, Pakistan and Bangladesh and contributes nearly one fourth of all new cases of cancer [3,4]. The majority (90%) of the cases reported of oral cancer (OC) are attributed to tobacco consumption in various forms in these regions [5]. There are several types of OC, but around 90% are squamous cell carcinoma [6].

Lipids are major cell membrane components which are important for various biological functions in body including cell growth and division of both normal and malignant cells [7]. Lipids get altered quantitatively in the serum during tumour development and may be considered as one of the biochemical markers used in early detection of cancer.

An association between serum lipids and lipoproteins with different cancers has been reported [8]. The possible influence of lipids in the pathogenesis of malignancies could be attributable to influence on the metabolism of malignant cells in terms of proliferation and incorporation in the membranes of neoplastic cells and lipids' function intercellular messengers or as mediators of the inflammatory reaction [9].

The search for molecular markers in body fluids for detecting cancer has been continuous. Serum lipids can be one such reliable marker. So, we undertook this study to estimate the serum lipid profile levels in OSCC patients and healthy controls and finding any statistically significant difference in their pathological levels compared to physiological levels can help us to establish the role of serum lipid markers in diagnosis and prognosis of Oral Cancer.

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Materials and Methods

Study Design

The study was done in the Department of Biochemistry in collaboration with the Department of Oncology of a tertiary level healthcare facility in North-western India. The study was initiated after obtaining necessary permissions from Research Review Board and Ethics Committee. Serum lipid profile levels were then measured in 45 patients of oral squamous cell carcinoma (OSCC) and compared with the lipid levels of an equal no. of age and sex matched healthy controls.

Patients were selected from the outpatient department of oncology diagnosed with oral squamous cell carcinoma in age group of 30-65 years, with no history of prior chemotherapy and radiotherapy and those who were willing to participate and give written informed consent for the study.

Patients with family history of hyperlipidemia, suffering from febrile diseases, major illness in the recent past or systemic disorders like uncontrolled diabetes, hypertension and thyroid disorders were excluded from the study. Pregnant females and subjects who were obese were also excluded from the study.

Sample collection and analysis

The blood samples of the patients was taken in plain vials in morning after 12 hour fasting. Serum was separated from samples after centrifugation at ~3000-4500 rpm and analyzed on fully automated analyzer Beckman coulter AU-680. Serum samples free from hemolysis were used for analysis.

Sampling Technique: For selection of subjects, simple random sampling technique was used by selecting every eligible subject.

Reagents: Serum Total cholesterol, HDL and triglyceride levels were estimated by enzymatic colorimetric method using in vitro diagnostic reagents. The reagents were ready to use. The unopened reagents were stable until the expiry date printed on the label when stored at 28°C. Opened reagents (routine) were stable for 90 days when stored in the refrigerated compartment of the analyzer.

Estimation of Total cholesterol: Enzymatic method (CHOD-PAP) [6,10-12].

Reagent composition: Buffer (ph 7.5), Cholesterol Oxidase, Cholesterol esterase, Peroxidase, Chromogen, Stabilizers, inactive ingredients and surface active agents.

Principle: Cholesterol esters were hydrolyzed by cholesterol esterase (CHE) into cholesterol and fatty acids. Cholesterol oxidase (CHO) catalyzed the oxidation of cholesterol into cholast 4-en-3-one and hydrogen peroxide. Catalyzed by peroxidase (POD), hydrogen peroxide oxidatively couples with 4-aminoantipyrine and phenol to produce red quinneimine dye, which has maximum absorbance at 510 nm. The intensity of red colour is proportional to amount of cholesterol in specimen.

Estimation of Serum HDL-Cholesterol: [6,10-12].

Reagent composition :

Reagent 1 Good‘s Buffer, Cholesterol oxidase, Peroxidase, Preservative, N,N-bis (4-sulphobutyl)-m toluidine disodium (DSBmT), Accelerator.

Reagent 2 Good‘s Buffer, Cholesterol esterase, 4-AAP, Detergent, Restrainer, Preservative, Ascorbic acid oxidase.

Calibrator : Lyophilized human Serum, Sodium Azide

Principle: The Method is in a two reagent format and depends on the properties of a unique detergent. This method is based on accelerating the reaction of cholesterol oxidase (CO) with non-HDL un-esterified cholesterol and dissolving HDL selectivity using a specific detergent.

In the first reagent, non-HDL unesterified cholesterol is subject to an enzyme reaction and peroxide generated is consumed by a peroxidase reaction with DSBmT yielding a colorless product. The second reagent consists of a detergent capable of solubilizing HDL specifically, cholesterol esterase (CE) and chromagenic coupler to develop color for the quantitative determination of HDL cholesterol. This may be referred to as the Accelerator Selective Detergent methodology.

Estimation of Serum Triglycerides: Enzymatic method (GPO-PAP method) [6,10-12].

Reagent composition: Triglycerides Enzyme Reagent, buffer (pH 7.5) Lipoprotein Lipase, Glycerol kinase, Glycerol phosphate oxidase, Ascorbate oxidase, Peroxidase, ATP, 4-Aminoantipyrine.

Principle: Triglycerides are hydrolyzed by lipoprotein lipase (LPL) into glycerol and fatty acids. Catalyzed by Glycerol kinase (GK), glycerol is phosphorylated to glycerol-3-phosphate. Glycerol-3-Phosphate is oxidized to dihydroxyacetone phosphate and hydrogen peroxide, in presence of glycerol phosphate oxidase (GPO). Catalyzed by Peroxidase (POD), Hydrogen peroxidase causes oxidation of phenolic chromogen (4 aminoantipyrine) and p-chlorophenol to a red colored compound. The intensity of the red colour is proportional to the amount of triglycerides in the serum.

Estimation of Serum VLDL-cholesterol and LDL-cholesterol: [6,10-12]

VLDL was estimated by TG/5 based on the average ratio to cholesterol in VLDL.

Serum LDL was estimated from the Freidwald and Fredrickson‘s (1972) formula, which is LDL=Total Cholesterol-[HDL+VLDL].

Results

Statistical Analysis: Quantitative data was analyzed in the form of Percentages, mean, standard deviation, and one-way ANOVA with Bonferroni correction and Scheffe post hoc at 95% confidence interval. Data thus collected was submitted to Microsoft excel 2007 worksheet in the form of master chart. These data were classified & analyzed with the help of Microsoft excel 2007 worksheet, statistical analysis was done with the help of Primer software. Levels of statistical significance were set at a P value < 0.05.

The participants were matched for gender in both the groups (OSCC and control group) and the mean age in both the groups was also almost similar (Table 1).

Table 1. Age and Gender Distribution of OSCC Patients and Control Group

Parameter	OSCC patients (n=45)	Controls (n=45)
Age (years)	51.13 ± 8.56	49.22 ± 9.21
Gender (Male: Female)	35:10:00	35:10:00

Table 2. Comparison of Mean Lipid profile levels between Oral Squamous Cell Carcinoma Cases and healthy controls

Lipids (mg/dl)	OSCC patients (n=45)	Controls (n=45)	P value
Triglycerides	84.18 ± 22.22	94.58 ± 26.06	<0.001 (S)
Total Cholesterol	113.24 ± 26.11	155.60 ± 25.98	0.39
HDL	34.2 ± 6.37	53.62 ± 7.14	< 0.001 (S)
LDL	62.21 ± 27.94	83.15 ± 23.75	< 0.001 (S)
VLDL	16.84 ± 4.44	18.91 ± 5.21	<0.001 (S)

*P-value as obtained on applying independent t test (S at p<0.05); S means significant.

There was a significant difference between the means of OSCC patients and controls in triglycerides, high density cholesterol, low density cholesterol and very low density cholesterol levels. There was no significant difference between means in total cholesterol levels (Table 2).

Discussion

In some malignant diseases, blood lipid levels undergo early and significant changes. Lowered levels of blood cholesterol in the proliferating tissues and in blood compartments may be due to the ongoing process of oncogenesis. The question arises whether hypolipidemia is considered to be a predisposing factor or a consequence of malignancy. However, earlier studies have shown that hypolipidemia may result primarily due to the direct lipid-lowering effect of tumor cells and secondarily to either malfunction of the lipid metabolism or antioxidant vitamins.

OSCC has become a global health problem with increasing incidence and mortality rates with variation in incidence in each geographic location in relation to age, gender, and habits.

The current study showed that mean age in control group was slightly lower than cases group. According to US National Cancer Institute SEER program the mean age of diagnosis of oral cancer is 65 years. Sankaranarayan et al. found that the peak age frequency of occurrence in India is at least a decade earlier than that described in the western literature [13]. Gupta et al observed an increase in the incidence of oral cancer in the younger (less than 50 years) age group [14]. Epidemiological study of oral cancer in India by Chattopadhyay et al and Mathew et al reported in developing countries, oral cancer may affect younger men and women more frequently than seen in the western world [15].

In our study, OSCC was seen between the age group of 4th to 6th decades of life with the mean age of 51 years. These results are well supported by studies such as Misra et al. in 2009 who reported a mean age of 53.15 [16]. Majority of the studies such as by Singh MP (2016) [17], Abdulla R (2018) [18], Tandon A (2018) [19] and Kumar GK (2019) [20] are consistent with our finding. Predictably in our study, the most affected age group was 51-60 years.

Similar to our study, most of the studies showed a male predominance which can be attributed to the socioeconomic norms favoring the easy availability of tobacco products to the male population. Males are more commonly affected compared to females by OSCC in both developed (male: female ratio 2.5:1) and developing (male: female ratio 3:1) countries, which may be due to easy acceptance of habits by males [21]. However, in recent time, this difference in gender distribution is reducing in the developed countries due to more females taking up tobacco-related habits including smoking [22].

This study confirmed previously established demographic factors such as age and gender predilection for OSCC in north Indian patients.

In the present study, the values evidently showed that oral cancer patients have significantly lower serum HDL and lower serum LDL values when compared with control group. This result is consistent with the result of study by Lohe et al. in 201 .[22]. It was postulated that low levels of cholesterol in the proliferating tissues and in blood compartments could be due to the process of carcinogenesis [22].

The results of the present study showed that serum TG, HDL, LDL and VLDL were significantly reduced in the OSCC group when compared with the reference values which is in agreement with studies reported by Ashutosh et al (2015) [23] and Garg et al (2014) [24]. Other studies have also reported decreased lipid levels in cancer patients but with variable lipid profile patterns as compared to control group.

Patel et al (2004) [7] found a significant decrease in TC, HDL, VLDL, and TG but not in LDL in patients with OSCC. Acharya et al (2016)[10] reported a significant decrease in TC, HDL, LDL, and VLDL but not for TG in patients with OSCC. Nydegger et al (1972) [25] observed a decrease in α - lipoprotein and cholesterol levels and was possibly due to increased catabolism of α – lipoprotein and cholesterol, decreased synthesis of α–lipoprotein and cholesterol by liver as the synthesis is affected by tumor metabolites.

Lipids are the most important cell membrane parts that are required for various biological functions, such as maintaining cell integrity, cell growth, and division of normal and malignant cells. There are three main competing hypotheses to explain the relation between low cholesterol and oral 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 [26].

The habit of tobacco consumption is a known etiologic factor for development of oral precancerous diseases and head/neck cancer [27]. 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. Lipid peroxidation further releases peroxide radicals. There is substantial evidence that the hydroxyl radical generated, can destruct tissue by initiation and propagation of lipid peroxidation by abstracting hydrogen from unsaturated fatty acids. This affects essential constituents of the cell membrane and might be involved in carcinogenesis/ tumor genesis [28].

In a study conducted by Fu-Chuan Chao et al [29], it was stated that hypolipidemia is a result of direct lipid lowering effect of tumor cells as these neoplastic cells directly utilize cholesterol for their own metabolism. The profound effect of hypolipidemia should be recognized and an early measure should be made to restore cholesterol levels to avoid conditions that may hasten morbidity and mortality in cancer patients. In another study conducted by Min-Ah Choi et al [30], it was suggested that hypocholesterolemia was secondary to decreased levels of serum antioxidative vitamins. Decrease in the level of antioxidative vitamins in serum results in increased number of free radicals which causes increased lipid peroxidation.

S Desai et al [31] proposed that free cholesterol within the tumor cells, is preferentially channeled into storage as cholesterol esters rather than being released from the cells to circulating HDL. This happens irrespective of whether the free cholesterol is arising from synthesis or uptake in the tumor cells. This mechanism explains the decreased levels of HDL in cancer patients. It has also been postulated in many studies that 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 [32]. Lower HDL levels may also be a sign of initial changes occurring in precancerous and neoplastic conditions. In the present study, a significant decrease was noticed in serum HDL in the study group of patients as compared to the control group. Similar findings were reported by Mujooet al [33], Anand et al [34], Meisel et al [35], and Granero Fernandez et al [36] in their studies to assess alterations in lipid profile levels.

In our study, Plasma triglycerides showed significant difference between the groups. Alexopoulos et al [22] found no significant difference in serum triglycerides between controls and patients.

Hypertriglyceridemia may also predispose to malignancy. Elevated triglyceride levels have been demonstrated in patients with several different types of cancer [22]. However; we found a significant decrease in serum triglycerides in cancer patients compared to the control group. The exact mechanism by which hypertriglyceridemia and decreased HDL-cholesterol concentration occurs in patients with cancer is not known. It has, however, been suggested that lipoprotein lipase (LPL) may regulate the clearance of TG from blood to tissue and its activity in white adipose tissue is decreased in patients with cancer, thus contributing to hypertriglyceridemia.

In the present study, serum LDL and serum VLDL levels were significantly lower when compared with the control group, whereas the difference was not statistically significant in the studies done by Mujoo et al [33] and Chalkoo et al [37] While Subbulakshmi et al. stated that the decrease in serum LDL and VLDL in squamous cell carcinoma cases may be due to enhanced lipid peroxidation due to decline in antioxidants [38].

Alsheikh-Ali and Richard Karas (Tufts University School of Medicine, Boston, MA) [39] showed there was a “significant and linear relationship” between LDL levels achieved and risk of new cancer cases. The “reverse-causality” hypothesis suggests that depressed LDL-cholesterol levels are the result of subclinical cancer, whereas the “forward causality” hypothesis states that depressed LDL cholesterol is a precursor to disease. The depressed LDL levels in our study may be due to the disease process.

The diagnostic implications of assessing lipid profile in smokers and tobacco and areca nut chewers might be that alteration in lipid profile may be the indication that the changes in the oral mucosa are occurring which may lead into premalignancy or malignancy. Thus, the estimation of lipid levels appears to be an easier and faster investigative method that should be included in routine diagnostic pathology services.

In conclusion, hence we conclude that the serum triglycerides, serum HDL, and serum LDL and serum VLDL levels are significantly lowered in patients with oral squamous cell carcinoma (OSCC) when compared with control group in our study and this reduction may be due to the significant changes in the cell integrity.

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