Alterations in serum lipid profile patterns in head & neck cancer and oral submucous fibrosis patients

Dr. Nupur Gupta¹
Dr. Ravi Prakash Sasankoti Mohan²
Dr. Sankalp Verma ³
Dr. Soumi Ghanta ⁴
Dr. Neha Agarwal ⁵
Dr. Navin Sankar ⁶

¹,⁴,⁵,⁶ MDS, Department of Oral Medicine Diagnosis & Radiology, Kothiwal Dental College & Research Centre, Kanth Road, Moradabad, India
² Professor and Head
Department of Oral Medicine Diagnosis & Radiology, Kothiwal Dental College & Research Centre, Kanth Road, Moradabad, India
³ Assistant Professor
Department of Oral Medicine Diagnosis & Radiology, Kothiwal Dental College & Research Centre, Kanth Road, Moradabad, India

Corresponding Author
Dr. Ravi Prakash S.M.
Department of Oral Medicine and Radiology
Subharti Dental College
Swami Vivekanand Subharti University, Delhi-Haridwar By-Pass Road, Meerut, Uttar Pradesh, India-250 002
Mobile: +91-9997119919
Email: sasan_ravi@rediffmail.com

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Abstract

Background: The changes in lipid profile have long been associated with cancer because lipids play a key role in maintenance of cell integrity. The present study evaluated alterations in serum lipid profile patterns in head & neck cancer & oral submucous fibrosis patients as well as the changes seen in their different stages.

Materials & methods: A total of 95 subjects who were clinically diagnosed as patients of head & neck cancer and oral submucous fibrosis & age and sex matched healthy controls were studied in the outpatient department of Kothiwal Dental College & Research Centre, Moradabad from October 2011 to November 2012. The lipid profile values including (i) serum cholesterol (ii) low density lipoprotein cholesterol (iii) high density lipoprotein cholesterol (iv) very low density lipoprotein cholesterol (v) serum triglyceride were estimated. Also the lipid profile values in TNM (primary tumor, regional lymph node, distant metastasis) staging in head & neck cancer patients & functional staging of oral submucous fibrosis patients were also estimated. These values were subjected for statistical analysis.

Results: Mean lipid levels were found to be maximum in oral cancer patients for all the parameters except serum high density lipoprotein cholesterol. For all the variables except serum low density lipoprotein cholesterol, minimum values were observed in oral submucous fibrosis patients. For serum low density lipoprotein cholesterol minimum values were observed in control group.

Conclusion: Our study found a direct relationship between lipid profile & cancer patients & an inverse relationship between lipid profile & oral submucous fibrosis patients. The findings strongly warrant an in depth study of alterations in serum lipid profile patterns in head & neck cancer & oral submucous fibrosis patients.

Keywords: Serum cholesterol, serum triglyceride, high density lipoprotein, low density lipoprotein, very low density lipoprotein, oral submucous fibrosis.

Introduction

The changes in lipid profile have long been associated with cancer because lipids play a key role in maintenance of cell integrity. Lipids are major cell membrane components essential for various biological functions including cell growth & division of normal & malignant tissues.¹,²

The habit of tobacco chewing with betel quid, tobacco smoking & alcohol consumption are the most important etiological factors for the development of oral submucous fibrosis and head & neck cancer.²,³
It is believed that tobacco carcinogens induce generation of free radicals & 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 cell membrane and might be involved in carcinogenesis/ tumorogenesis. Because of the lipid peroxidation, there is a greater utilization of lipids including total cholesterol, lipoproteins & triglycerides for new membrane biogenesis. Cells fulfill these requirements either from circulation, by synthesis through the metabolism or from degradation of major lipoprotein fractions like high density lipoprotein (HDL), low density lipoprotein (LDL) or very low density lipoprotein (VLDL). 51

Staging of the Head & neck cancer is done clinically on the basis of TNM classification & Broders histopathological grading, on the basis of different degree of differentiation. Both these staging have several shortcomings & might lead to spurious results. The treatment also varies according to the staging & grading of malignancies & may lead to intersubjective discrepancies. There is no such marker which can work as a reflection in the various stages of malignancy.

In the TNM staging of head & neck cancer, the size of the primary tumour, its invading structures and regional lymph nodes involvement cannot be properly assessed only on the basis of clinical examination & can cause bias. Conventional radiography provides limited information to stage head & neck malignancies. To know the exact extent of the tumor & the involvement of deep lymph nodes, investigations like CT scan & MRI is needed. Distant metastasis is also difficult to assess.

According to Broders histopathological grading, there can be difference in degree of differentiation at different locations at variable time span in the same patient. That leads to controversial interpretations according to different pathologist on the basis of dysplastic features leading to variability in the treatment plan.

So, there is a need of a prognostic indicator which is easy, economic, time-effective and can give consistent results in head & neck cancer and oral submucous fibrosis patients. The lipid profile pattern estimation can work as a valuable prognostic indicator in head & neck cancer & oral submucous fibrosis patients & might help in assessing the prognosis of such patients in future generations.

**Methods**

**Study design:**

A total of 95 subjects who were clinically diagnosed as patients of head & neck cancer and oral submucous fibrosis & age and sex matched healthy controls on the basis of detailed case history were selected from the Outdoor Patient Department of Kothiwal Dental College & Research Centre. Before taking the fasting blood sample, written consent was taken from every patient. After taking consent the venous blood sample was collected from all patients to estimate the lipid profile levels. Blood sample was taken after 8 hours of fasting. The lipid profile values including (i) serum cholesterol (ii) low density lipoprotein cholesterol (iii) high density lipoprotein cholesterol (iv) very low density lipoprotein cholesterol (v) serum triglyceride were estimated. These values were subjected for statistical analysis.

The methods used are:

- For serum cholesterol: Modified Roesechau’s method (cholesterol oxidase – papanicolaou method) Cholesterol reagent, cholesterol standard & AQUA-4 kit are used which are manufactured by Transasia Bio-medicals
- For serum triglyceride: Method of Wako with modifications by McGowan et al and Fossati et al (glycerol phosphate oxidase – trinder method) Triglyceride reagent, triglycerides standard & AQUA-4 kits are used which are manufactured by Transasia Bio-medicals
- For high density lipoprotein cholesterol: Phosphotungstate method. Reagent1 (enzymes/ chromogen), reagent1A (buffer), reagent2 (precipitating reagent), standard (high density lipoprotein cholesterol 50mg/dl) are used manufactured by Siemens Healthcare Diagnostics
- For low density lipoprotein cholesterol: Friedewald’s equation is used: Low density lipoprotein cholesterol = total cholesterol – (triglyceride/5 – high density lipoprotein cholesterol)
- For very low density lipoprotein cholesterol: Very low density lipoprotein cholesterol = triglyceride/5

The statistical analysis was done using SPSS (Statistical package for social sciences) version 15.0 statistical analysis software. The values were represented in number (%) and mean ± standard deviation.

**Results**

A total of 95 subjects were enrolled. Distribution of subjects in different groups has been shown in Table 1. Out of 95 subjects enrolled in the study, a total of 30 (31.6%) subjects were normal healthy individuals with sound oral health. These subjects comprised the control group of the study. A total of 30 (31.6%) patients were clinically confirmed cases of oral submucous fibrosis and comprised the Study Group I of the study and remaining 35 (36.8%) subjects were clinically confirmed cases of...
oral squamous cell carcinoma and comprised the Study Group II of the study. (Table 1)

**Comparison of Mean Lipid levels in different groups (Table 2)**
Mean lipid levels were found to be maximum in Study Group II for all the parameters except S. HDL. For all the variables except S.LDL, minimum values were observed in Study Group I. For S. LDL minimum values were observed in Control group. Analysis of variance (ANOVA) revealed statistically significant intergroup difference for S. Cholesterol, S. HDL and S. LDL. Statistically, there was no significant intergroup difference for S. Triglyceride and S. VLDL.

**Comparison of Mean Lipid Levels (Table 2a)**
For S. cholesterol, statistically significant difference was observed between Control Group and Study Group II only. For S. triglyceride, none of the differences were found to be significant statistically. For S. HDL, all the three between group comparisons were significant statistically (p<0.05). For S. VLDL, none of the between group differences were significant statistically (p>0.05).

**Comparison of Derangement of Lipid values in different groups (Table 3)**
Among controls except for 1 case with low S. HDL none of the cases showed any derangement for any of the lipid parameters. In Study Group I, a total of 4 (13.3%) cases had S. cholesterol level >200 mg/dl, 5 (16.7%) each had S. Triglyceride and S. VLDL levels above the cut-off, 3 (10%) had S. HDL <35 mg/dl and 2 (6.7%) had S. LDL levels >130 mg/dl. In Study Group II, 7 (20%) patients had S. Cholesterol levels >200 mg/dl, 6 (17.1%) had S. triglyceride levels >200 mg/dl, 1 (2.9%) had S. HDL <35 mg/dl, 8 (22.9%) had S. VLDL levels >38 mg/dl and 3 (8.6%) had S. LDL >130 mg/dl. Statistically significant difference among groups was observed for S. cholesterol and S. VLDL levels respectively (p<0.05).

**Distribution of Patients in Study Group I according to OSMF Stage (Table 4)**
A total of 10 (33.3%) patients each had Stage I, Stage II and Stage III oral submucous fibrosis respectively.

**Comparison of Mean Lipid values in different stages of OSMF (Table 5)**
S. Cholesterol and S. HDL levels were maximum in Stage I patients while S. Triglyceride and S. VLDL levels were maximum in Stage II. S. LDL levels were maximum in Stage III. None of the intergroup differences were significant statistically (p>0.05).

**Comparison of patients with deranged lipid values in different stages of OSMF (Table 6)**
For all the parameters except S. HDL, Stage II patients had higher proportion of patients with deranged values as compared to stages I and III but none of the associations were significant statistically.

**Distribution of Patients in Study Group I according to TNM Stage (Table 7)**
In Study Group II, maximum number of patients (n=10; 30.8%) were TNM stage III, 10 (30.8%) patients each were TNM stage II and 8 (27.7%) each were TNM stage I and IV respectively.

**Comparison of Mean Lipid values in different stages of Oral SCC (Table 8)**
S. Cholesterol, S. TG and S. VLDL levels were maximum in Stage I patients while S. HDL levels were maximum in Stage II. S. LDL levels were maximum in Stage IV. Except for S. TG and S. VLDL levels none of the differences were found to be significant statistically. S. TG and S. VLDL levels were found to be significantly higher in Stage I as compared to other stages.

**Comparison of patients with deranged lipid values in different stages of Oral SCC (Table 9)**
For all the parameters except S. LDL, Stage I patients had higher proportion of patients with deranged values as compared other stages for S. LDL, Stage IV had maximum proportion of patients with derangement. Intergroup differences were found to be significant statistically too for S. Triglyceride, S. HDL and S. VLDL only.

**Discussion**
Head & neck cancer is one of the leading causes of morbidity & mortality & habit of tobacco consumption is a known etiological factor for development of oral submucous fibrosis & head & neck cancer. Patients with oral submucous fibrosis have also been reported to show a significant tendency to develop cancer. In some malignant
diseases, blood cholesterol undergoes early & significant changes. The mechanism for the link between cancer & cholesterol remains controversial. The dates from studies are confusing because both hypolipidemia & hypercholesterolemia might be connected with malignancy. Therefore, the present study was done to determine the alterations in serum lipid profile patterns in head & neck cancer & oral submucous fibrosis patients. Our study did not coincide with the studies of Patel et al, their results showed a significant decrease in plasma total cholesterol & HDLC in cancer patients as well as in patients with oral precancerous condition as compared to controls. In our study, the serum cholesterol, triglyceride, S.LDL, S.VLDL except S.HDL showed a significant increase in cancer patients. In oral submucous fibrosis patients all variables except S.LDL had minimum values. Studies by Chalkoo et al found that there is a significant decrease in serum cholesterol & LDLC whereas serum triglyceride & HDLC were slightly increased in some patients with OSMF. This study was partially similar to our study in which all variables except S.LDL had minimum value. Some of the previous studies stated that serum cholesterol levels were inversely associated with incidence of cancer. Our study performed on oral submucous fibrosis also showed inverse relation between S. cholesterol, S.HDL, S. triglyceride, S. VLDL & oral submucous fibrosis patients, these changed levels might indicate the progression of these lesions towards malignancy.

Studies by C. G. Alexopoulos et al found that there is significantly lower value of total cholesterol & LDLC in men with cancer (lung & haematological cancer) as compared to controls. These results were in contrast to our study performed on oral submucous fibrosis patients. Their study also found values of TG levels which were not statistically significant between groups, similar to our study.

Studies done by Ghosh et al & Chawda et al showed that there is a significant decrease in total lipids, cholesterol & HDL in patients with oral cancer as compared to controls. These studies were in contrast to our study which revealed higher values of all lipid profiles except S.HDL in cancer patients.

Shally Gupta et al & Nayak P et al performed their study on oral precancerous lesions & condition & found a significant decrease in plasma total cholesterol, HDLC & triglycerides. This was in accordance with our study on oral submucous fibrosis patients.

In a study done by Arthur Schatzkin Robert N. Hoover et al, an inverse association has been observed for low base line serum cholesterol & cancer of the colon. In the study done by Omoti et al the mean serum cholesterol & LDLC in the cancer patients were significantly lower than those of controls. However, the mean serum triglyceride of the patients was significantly higher than the controls. This was in contrast to our study in which the S. cholesterol & LDLC showed maximum levels.

Study done by Nydegger et al was in contrast to our study which revealed that serum triglycerides & cholesterol levels were markedly decreased in cancer patients.

Study done by Ray & Husain et al was similar to our study in which plasma total cholesterol, LDLC & triglycerides were found to be significantly elevated among breast cancer patients as compared to the controls. On the other hand, plasma HDLC concentration was significantly reduced in breast cancer patients similar to our study. Jacobs et al in their study concluded that there was no association between total cholesterol or its subfractions & risk of aggressive prostate cancer. Eichholzer et al in their study concluded that increased cancer mortality risk with low plasma cholesterol were attributed in part to the effect of preexisting cancer.

A total of 10 patients each had stage I, stage II & stage III oral submucous fibrosis respectively were included in our study. In the study done by Ravi Mehrotra et al, divided the oral submucous fibrosis patients on the basis of clinical grading of trismus & found that 5 patients had grade I, 34 had grade II & 26 had grade III stage of oral submucous fibrosis among 65 patients.

In the study done by Chalkoo et al, division was done according to the clinical grading of limited mouth opening & found that 5 patients were of grade I, 12 had grade II & 3 had grade III among 20 oral submucous fibrosis patients.

According to S. M. Haider et al, oral submucous fibrosis is diagnosed on clinical criteria including mucosal blanching, burning, hardening & the presence of characteristic fibrous bands & is associated with gradual inability to open the mouth. Mouth opening is an objectively verifiable criterion by which severity of the disease can be assessed (functional stage). Clinically, it may be classified by the site of the fibrous bands (clinical stage). The purpose of their study was to stage the severity of the disease (functional staging) using an objective measure (interincisal opening) & to study its relationship to clinical staging.

**Clinical & functional stage:**

**Clinical stage**

1. Faucial bands only
2. Faucial & buccal bands
3. Faucial, buccal & labial bands

**Functional stage**

A. Mouth opening ≥ 20mm
B. Mouth opening 11 -19mm
C. Mouth opening ≤ 10mm
In their study, as far as functional stage was concerned, 75 (26%) could open their mouth 20mm or more (stage A), 192 (67%) could open their mouth between 11 to 19mm (stage B) & 21 (7%) could open their mouth 10mm or less. (stage C). [21]

We divided the clinical stages of OSMF based on the study done by Nagesh & Bailoor (1993) who divided the clinical stages of OSMF & measured the normal distance between central incisor tips. The classification is as follows:-

**Stage I** (early OSMF): mouth opening:
- Males – 35 to 45mm
- Females – 30 to 42mm

**Stage II** (moderate OSMF): mouth opening:
- Males – 24 to 34mm
- Females – 20 to 28mm

**Stage III** (severe OSMF): mouth opening:
- Males – 12 to 23mm
- Females – 10 to 19mm [22]

In study group II, maximum number of 10 patients were TNM stage III; 9 patients each were TNM stage II & 8 each were TNM stage I & IV respectively. Doshi Neena P et al categorized & noted the size of the primary tumor into T1 to T3 (T4 tumors were excluded from the study) according to AJCC TNM stage for oral cavity & lip cancer. Number of involved nodes & size of involved lymph nodes was noted & categorized into Nx to N3. This was partially similar to our study, but in our study we also included stage IV of TNM staging patients. [23]

The study similar to our study was done by S. Manoharan et al where patients were categorized into three different groups of 16 each (stage II, III & IV) according to TNM (tumor, node, metastasis) system of cancer classification. Sixteen age matched healthy males were also investigated as control. [3] Chawda et al categorized the cancer patients 10 subjects, each of well differentiated carcinoma, moderately differentiated & 5 patients of poorly differentiated carcinoma. [13]

**Conclusion**

From this study it is evident that there are definite underlying biochemical alterations in serum lipid profile patterns in patients of oral cancer & oral submucous fibrosis when compared with healthy individuals. This can be a pilot study to identify the bio-chemical pathways that can be explored further to signify them as prognostic markers; so that proper awareness, motivation and treatment measures can be undertaken at appropriate time to decrease the mortality & morbidity.

**References**


<p>| Table 2: Comparison of Mean Lipid levels in different groups (mg/ml) |
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Table 5: Comparison of Mean Lipid values in different stages of OSMF (mg/ml)

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Table 8: Comparison of Mean Lipid values in different stages of Oral SCC (mg/ml)

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Table 9: Comparison of patients with deranged lipid values in different stages of Oral SCC (mg/ml)

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<td>2 20.0</td>
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<td>5 62.5</td>
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Bar graph 1: Distribution of Subjects in different groups

Bar graph 4: Distribution of Patients in Study Group I according to OSMF Stage
Bar graph 3: Comparison of Derangement of Lipid values in different groups (mg/ml)

Bar graph 6: Comparison of patients with deranged lipid values in different stages of OSMF (mg/ml)

Bar graph 7: Distribution of Patients in Study Group I according to TNM Staging