Correlation of Serum Lipid Profile in Patients with Oral Submucous Fibrosis in Gulbarga, India
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ABSTRACT

Background: Oral submucous fibrosis (OSMF) is a chronic disease of the oral cavity. Changes in the serum lipid profile have long been associated with malignancies as Lipids play a key role in maintenance of cell integrity. Aim: To evaluate the alterations in extended lipid profile parameters in patients with OSMF. Materials and Method: In this hospital-based study, 30 clinically diagnosed and histopathologically proven patients of OSMF and 10 healthy controls were compared. In these groups, serum lipids including: (i) total cholesterol (TC), (ii) high density lipoprotein cholesterol (HDL), (iii) low density lipoprotein cholesterol (LDL) (iv) triglycerides and (v) very low density lipoprotein cholesterol (VLDL) were analyzed. Results: A significant decrease in all the lipid profile parameters was observed in OSMF patients as compared to the controls. Thus, an evidence of alterations between plasma lipid levels and OSMF was found. There was an overall correlation of serum lipid profile and histopathological grading. As the histopathological grading increased there was progressive decrease in all the parameters of lipid profile. Conclusion: The lower levels of plasma cholesterol and other lipid constituents in patients might be due to their increased utilization. There was an overall significant correlation of serum lipid profile and histopathological grading.

Keywords: Oral Submucous Fibrosis; Arecanut; Serum Lipid Profile.

Introduction

Oral submucous fibrosis (OSMF) is an insidious chronic disease affecting any part of oral cavity and sometimes the pharynx and occasionally preceded by or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic changes in the lamina propria with epithelial atrophy leading to stiffness of mucosa and causing trismus and inability to eat. This disease occurs most commonly in South East Asia but cases have been reported worldwide in countries like Kenya, China, UK, Saudi Arabia and other parts of the world. Over the years, the incidence of OSMF has increased manifold in various parts of the Indian sub-continent including the North Karnataka and Gulbarga region. The strongest risk factor for OSMF is the chewing of betel quid containing areca nut. The amount of areca nut in betel quid and the frequency and duration of chewing betel quid are clearly related to the development of OSMF. The direct contact of the quid mixture with oral tissues results in their continuous irritation by various components, including biologically active alkaloids (arecoline, arecaidine, arecolidine, guvacoline, guvacine, flavonoids (tannins and catechins) and copper. Consumption of chillies, nutritional deficiency, chewing tobacco, smoking, alcohol, genetic susceptibility, altered salivary constituents, autoimmunity and collagen disorders may be involved in the etiopathogenesis of this condition. The pathogenesis of OSMF is not well established, although a number of possible mechanisms have been suggested. Pathogenesis is believed to involve juxta-epithelial inflammatory reaction and fibrosis in the oral mucosa, probably due to increased cross-linking of collagen through up-regulation of lysyl oxidase activity. Fibrosis, or the buildup of collagen, results from the effects of areca nut, which increases collagen production (e.g., stimulated by arecoline, an alkaloid) and decreases collagen degradation. Thus, OSMF is now considered a collagen metabolic disorder. Excessive use of areca nut may also 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 tumorogenesis. The features described are progressive narrowing of the mouth, blanching of the oral mucosa, pain and burning sensation on taking food, hypomobility of the soft palate and tongue, loss of gustatory sensation and occasional mild hearing impairment due to the blockage of the Eustachian tube. Lipids are major cell membrane components essential for various biological functions including cell growth and division of normal and malignant tissues. They are a heterogeneous group of compounds related more by physical than chemical properties. Alteration in the circulatory cholesterol levels has been found to be associated in the etiology of breast cancer and colorectal cancer. However, only a few reports are available on plasma lipid profile in head and neck cancers and very few on the precancerous conditions.

The aim of this study was to evaluate and correlate serum lipid profile in OSMF patients in Gulbarga population.

Materials and Methods

The study sample consists of a randomly selected 40 subjects from the outpatient Department of Oral Medicine and Radiology of Al-Badar Rural Dental College and Hospital, Gulbarga. The selection criteria includes patients using areca nut and areca nut containing products, tobacco mixed with areca nut in different forms, and alcohol, were satisfying the clinical criteria as given in literature such as presence of burning sensation, blanching of the oral mucosa, restricted mouth opening, restricted tongue protrusion and palpable fibrous bands. The study was conducted by strictly adhering to the ethical protocols and written consent from sample population. Subjective and objective parameters were recorded for these patients. Functional staging of OSMF was done according to Haider et al, i.e., Stage A- mouth opening greater than
or equal to 20 mm, Stage B- mouth opening 11 -19 mm, Stage C- mouth opening less than or equal to 10 mm. After clinical diagnosis and functional staging, patients were subjected to incisional biopsy of the buccal mucosa and the histopathological grading was done according to Pindborg and Sirsat.12 The study population was divided into two groups, Group I: 30 subjects with histopathologically confirmed diagnosis of oral submucous fibrosis and Group II (Control group): 10 healthy subjects with no oral precancerous and cancer conditions and do not show any signs and symptoms of OSMF. Exclusion criteria includes patients under treatment for OSMF, patients not ready for incisional biopsy, oro-mucosal disorders with clinical features same as OSMF and any systemic disorders which can cause similar symptoms. After histopathological confirmation the patients were recalled with a minimum of 12 hours of fasting. Venous blood (3ml) was collected using a sterile disposable syringe and the blood sample was allowed to clot, serum was extracted and stored at 4°C till subjected for blood examination for complete Lipid profile, of Total cholesterol (TC), Triglycerides (TG), High density lipoprotein (HDL) cholesterol, Low density lipoprotein (LDL) cholesterol, Very low density Lipoprotein (VLDL) cholesterol.

Method of Estimation: The values for TC, TG, HDL cholesterol were estimated by Roche COBAS III Auto-analyzer and LDL cholesterol, was estimated by using friedewald formula (TC-TG/5+HDL=LDL) and VLDL cholesterol was calculated as, Serum triglycerides / 5. The statistical analysis was done by using ANOVA, Student’s ‘t’ test and Chi Square test. For all test ‘p’ value of 0.05 or less was utilized for statistical significance.

Results

Out of the 30 patients, 6(20%) patients were in their second decade of life, maximum numbers of patients 18(60%) were in the third decade of life, 3(10%) were in the fourth decade and 3(10%) patients belonged to fifth decade of life. The age of the patients was between 15-50 years. The mean age of the 30 patients was 26.43±8.9 years. Among the 30 patients 27(90%) were males and 3(10%) were females. The control group comprised of 10 subjects with age range of 25-38 years and mean age 30.4±3.9 years.

Habit of tobacco consumption in one or other form is highly prevalent in the region. According to the habits, 12(40%) patients were gutkha chewers, 8(27%) were cigarette smokers as well as gutkha chewers, 7(23%) were only Arecanut chewers, 2(7%) were Arecanut chewers and cigarette smokers and 1(3%) patient was gutkha chewer as well alcohol consumer. Based on clinical examination 22 patients (73%) had blanching of the oral mucosa, 21(69%) had palpable fibrous bands, 24(79%) had restricted mouth opening, 12(40%) had burning sensation of mouth, and 6(19%) had restricted tongue protrusion. On functional staging, 7 patients (23%) belonged to stage A (≥20mm) mouth opening, 19(64%) belonged to stage II (<20mm), and 4(13%) patients belonged to stage IV (≤10mm) mouth opening. All the five parameters of plasma lipid were estimated and compared for both control group and study group (Table 1). In control group mean lipid profile parameters were, TC 188.37±36.4, HDL cholesterol 43.32 ± 6.48, LDL 129.27± 32, TG 145.15 ± 55.2 and VLDL cholesterol 28.06 ± 7.68 respectively. In study group mean lipid profile parameter were, TC 164.44 ± 33.2, HDL cholesterol 34.48±5.52, LDL cholesterol 118.8 ± 25.68, TG 121.04 ± 29.6 and VLDL cholesterol 34.48±5.52.
cholesterol $24.27 \pm 5.91$ respectively. The mean values for all the parameters of lipid profile for the study group showed a progressive decrease when compared to the normal subjects. Statistically the lipid profile parameters of (TC), (LDL), (TG) and (VLDL) showed $P<0.05$ which is statistically not significant whereas value of HDL showed $p<0.01$ which is statistically highly significant.

Correlation between histopathological grading and lipid profile parameters showed, 4(13%) patients belonged very early stage with TC level of 176.05, TG levels of 127.80, LDL levels of 117.26, HDL levels of 36.51 and VLDL levels of 25.56. 9(30%) patients belonged to Early stage with TC levels of 169.21, TG levels of 127.17, LDL levels of 119.26, HDL levels of 34.49, and VLDL levels of 25.43. 12(40%) patients belonged moderately advanced stage with TC levels of 165.2, TG levels of 117.02, LDL levels of 130.16, HDL levels of 34.82 and VLDL levels of 23.40. S(17%) belonged to advanced stage with TC levels of 146, TG levels of 98.25, LDL levels of 113.35, HDL levels of 31.75 and VLDL levels of 19.65 (Table 2). Co-relation coefficient values for histopathological grading and Lipid profile parameters were calculated which showed for TC $r=-0.944$ with p-value as 0.056 which shows a significant negative correlation. For TG $r=-0.925$ with p-value as 0.075 which shows significant negative correlation, for LDL $r=-0.015$ with p-value as 0.985, the correlation was not significant. For HDL $r=-0.914$ with p value as 0.086 which shows significant negative correlation, for VLDL $r=-0.925$ with p-value as 0.075 which shows significant negative correlation.

**Discussion**

Oral submucous fibrosis is one of the most poorly understood and unsatisfactorily treated diseases. An estimated 2.5 million people suffer from the disease in India. Areca nut chewing, tobacco smoking and hypersensitivity to chillies are the precipitating/causative agents in genetically predisposed patients. The importance of this disease lies in its inability to open the mouth and dysplasia giving rise to malignancy. The incidence of malignant change in patients with OSMF ranges from 2 to 10%. In general when younger the patient’s age, more rapid the disease progression. All the available treatments give only symptomatic relief, which too is short lived.\(^{13}\)

Cholesterol is an amphiphatic lipid and as such is an essential structural component of all cell membranes and of the outer layer of plasma lipoproteins. It is present in tissues and in plasma lipoprotein either as free cholesterol or combined with a long-chain fatty acid, as cholesteryl ester. It is synthesized in many tissues from acetyl-CoA and is ultimately eliminated from the body in the bile as cholesterol or bile salts.\(^{13}\) Lipoprotein transports free cholesterol in the circulation, where it readily equilibrates cholesterol in other lipoproteins and in membranes.\(^{14}\)

Cholesterol is often found distributed non-randomly in domains in membranes.\(^{15}\) Recent observations suggest that cholesterol exerts many of its actions by maintaining a specialized type of membrane domain, termed “lipid rafts” in a functional state. Lipid rafts are enriched in cholesterol and sphingo lipids, and have been thought to act as platform through which signal transduction events are coordinated and pathogens gain entry to infect host cells.\(^{17}\) In some malignancies, serum cho lesterol undergoes early and significant changes. Low levels of cholesterol in the proliferating tissues and in blood compartments could be due to the rapidly dividing cells in malignancies. Several prospective and retrospective studies have shown an inverse association between blood lipid profiles and different cancers. Some scientists have observed an inverse trend between lower serum cholesterol and head and neck cancer as well as esophageal and colon cancers.\(^{16}\) Hence this study is undertaken to evaluate and correlate serum lipid profile in precancerous condition (OSMF) in Gulbarga population.

In our study majority of the patients i.e. 18 were in the age range of 21-30 years. Thus most of our patients were in the second and third decades of life. This is in agreement with the previous study results in literature.\(^{11,17-21}\) However, Zhang et al from China suggested that the 30 to 49 years age group was the most commonly affected. This observation is also different from that of Pindborg et al who reported the maximum number of OSMF cases in the age group of 40-49 years in their study. Our study shows that the younger age group is more habituated for Gutkha in one or other forms and are susceptible for OSMF. In general it was found that, of the 30 OSMF subjects 20 patients chewed either gutkha alone or in combination. Our observations of 20 patients who chewed gutkha are comparable to previous observations\(^{17}\). The criteria of recording the signs and symptoms, and functional staging showed no noteworthy differences to previous studies. The mean values for all the parameters of lipid profile for the study group showed a significant decrease when compared to normal subjects. The results of the present study are similar to the studies\(^{22-23}\) showing a significant decrease in plasma total cholesterol, HDLC, and triglycerides were observed in the patients with the precancerous lesions and conditions as compared to the controls.\(^{24}\)

The significant decrease might be a consequence of disease that is mediated by utilization of cholesterol for membrane biosynthesis. Some of the studies\(^{25,26}\) showed increase in triglycerides levels in OSMF patients and some\(^{26}\) observed elevated triglycerides levels in cancer patients but one study\(^{27}\) results observed non significant difference in serum triglycerides between controls and patients. In this study there was decrease in HDL levels with p value <0.01 which was highly statistically significant where as levels of TC, TG, LDL, and VLDL with p value > 0.05 were statistically non significant. On contrary other studies\(^{25,27-29}\) did not find any significant change in the HDL levels. None of the previous studies and literature correlated between histopathological grading and lipid profile parameters. Our study is first of its kind, which showed that as the histopathological grading increased there was progressive decrease in all the parameters of lipid profile.

**Conclusion**
The change in lipid levels may have a diagnostic or prognostic role in the early diagnosis or prognostication of this premalignant condition (OSMF). The findings strongly warrant an in-depth study of alterations in plasma lipid profile in these patients. In the present study, it appears that the lower serum lipid profile parameters may be considered as a useful indicator for changes occurring in the OSMF, which can be used to prevent further progress of the disease. There can be a correlation of histopathological grading and lipid profile in OSMF patients but, the present findings are drawn by a smaller sample size but the findings strongly warrant an in-depth study on a larger sample size.

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