ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at: www.ijdsir.com

Volume – 5, Issue – 4, August - 2022, Page No. : 263 - 270

A comparative study of serum lipid levels in oral premalignant lesions and premalignant conditions

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Citation of this Article: Dr Sumantro Banerjee, Dr Surajit Bose, Dr Jayanta Chattopadhyay, "A comparative study of serum lipid levels in oral premalignant lesions and premalignant conditions", IJDSIR- August - 2022, Vol. – 5, Issue - 4, P. No. 263 – 270.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Different studies conducted recently show an inverse relationship between serum lipid profile and the chances of developing carcinoma and premalignant lesions among both smoked and smokeless tobacco users and diabetic patients. The lower levels of serum lipid may be attributed to their increased usage by malignant cells for developing new cell membranes. Serum lipid levels have also shown to decrease with disease progression which may pose to be a useful indicator for detecting the disease at an early stage, and for a better prognosis of premalignant lesions and conditions. In this observational study, serum lipid profiles of healthy participants and individuals with premalignant lesions and conditions were performed. Mean values of TC, TG, HDL, LDL and VLDL were compared among the three groups. The mean TC levels of group I, group II, and group III were 172.08 mg/dl, 171.43 mg/dl, and 179.15 mg/dl respectively. The Control group had significantly higher mean TC than group I and group II. The mean TG levels among group I group II, and group III were 149.05mg/dl, 199.05mg/dl and 113.26mg/dl respectively. The differences between the three groups were significant. The mean HDL levels were 45.81 mg/dL, 46.57 mg/dL and 41.83 mg/dL among the groups and significantly lower among the controls. Changes in lipid profile were found in oral premalignant disorders which can be used for early detection of carcinoma helping in early diagnosis. A larger sample size is needed to make the test an efficient prognostic tool in life-threatening conditions.

Keywords: Lipid Profile, Oral Premalignant Diseases, Tobacco, Biomarkers

Introduction

Lipids are essential biomolecules for the maintenance of various biological functions including stabilization of deoxyribonucleic acid helix, cell growth and division in normal as well as in malignant tissues. Lipids molecules are carried in body fluids with the help of lipoproteins [1]. These lipoproteins additionally transport cholesterol, which is also a type of lipid, from tissue cells to the liver. They serve as energy storage sources and participate in signalling pathways. Lipids are classified broadly based on their composition into simple, complex and derived lipids. Based on their functions, lipids are divided into storage, structural, cofactors, signals and pigments. Recent studies have shown chronic heart disease to play an important role in malignancy of which cholesterol is an important risk factor [2]. The incidence of premalignant lesions and conditions are most prevalent in Central and South-East Asian countries with oral cancer being one of the 10 most common carcinomas. The prevalence is relatively higher among men, older people, people with low literacy levels and low income, with tobacco and alcohol consumption being the major causal factors [3]. The incidence rate of precancerous lesions is 10 cases per 100,000 population with about 36,000 deaths due to oral cancer with a mortality rate of about six per 100,000 people according to a survey taken in India in 2012 attributing to a major health issue [3]. Easy detection of pre-malignant lesions can be done by visual inspection and palpation by health care professionals. However, biopsy followed by histopathological analysis remains the diagnostic gold standard.

Tobacco usage increases the risk of oral cancer by five to nine times as shown in recent epidemiological studies [4]. The World Health Organization (WHO) predicted that deaths caused by tobacco consumption will surpass 1.5 million annually. One hundred million people have a habit of chewing tobacco in India and Pakistan and 82000-90000 youngsters commence smoking worldwide every day which has led to an increase in tobacco use from 300 million per year in 1920 to 5.5 trillion in 2020. Women who are long-time users of snuff have a risk of being affected by oral cancer four times more as shown in a study conducted in the Southern United States [5]. Oral cancers are most often preceded by premalignant lesions or conditions including oral submucous fibrosis (OSMF), oral leukoplakia and lichen planus (LP).

Lipid metabolism initiates in the oral cavity and continues in the small intestine by utilizing bile salts and with the help of peristalsis. Next, the degraded lipids enter the bloodstream to be carried to the muscles and adipose tissues for storage or metabolism. Malignancy shows abnormalities in lipid metabolism including an inverse relationship between blood lipid profiles and different types of cancer, and prominent alterations of cholesterol and triglycerides in nascent stages of malignancies. Additionally, the production of polyunsaturated fatty acids and specific fatty acids which are required during protein modification are affected during lipid metabolism in cancer patients. Moreover, recent research has identified that malignant tissues can synthesize lipids and use exogenous fatty acids to produce membrane and oncogenic signalling lipids [6]. Therefore, lipid Metabolism and Lipid Profile Patterns in Oral Cancer Lipids in malignant tumours are not only necessary for providing the membrane constituents of proliferating cells but are also needed for energetic, biophysical and signalling pathways that drive tumorigenesis [7-8]. The serum lipid profile analysis includes total cholesterol, high-density lipoproteins, low-

density lipoproteins, very low-density lipoproteins and triglycerides. Different studies conducted recently show an inverse relationship between serum lipid profile and the chances of developing carcinoma and premalignant lesions among both smoked and smokeless tobacco users and diabetic patients [9 - 13]. The lower levels of serum lipid may be attributed to their increased usage by malignant cells for developing new cell membranes. Serum lipid levels have also shown to decrease with disease progression which may pose to be a useful indicator for detecting early stages and prognosis of premalignant lesions and conditions. Gupta and colleagues in 2014 evaluated alterations in serum lipid profile patterns in head & neck cancer & oral submucous fibrosis patients at different stages of the diseases [14]. A direct relationship between lipid profile and cancer patients was identified, more specifically, the mean lipid levels of all components were found highest in oral cancer patients except for high-density lipoprotein. Although there is a growing number of evidence on the use of lipid profiles as a diagnostic tool, there has been no unanimous agreement because of the lack of good-quality studies. Additionally, there is currently a dearth of recent studies in West Bengal. Malignant and premalignant lesions if diagnosed early by comparing and evaluating the serum lipid levels will have multiple advantages. These include cost-effectiveness, operational advantages due to the ease of testing and patient compliance because of the non- invasive nature of tests [15]. To compare and evaluate serum lipid levels among patients with oral premalignant lesions and conditions in West Bengal is the aim of the study.

Material and Methods

In this observational cohort study, sixty outdoor patients seeking dental treatment from the Department of Oral and Maxillofacial Pathology at Kusum Devi Sunderlal Dugar Jain Dental College & Hospital, Kolkata were divided into three groups, precancerous lesions, precancerous conditions and healthy control consisting of 20 patients each. Patients without a history of any underlying diseases and having clinical and histopathological confirmation of premalignant lesions and conditions were included in the study. Patients who were obese or overweight, pregnant, above 65 years of age, with a history of hyperlipidemia or on topical/ systemic medications for oral premalignant lesions and conditions were excluded.

Ethical clearance was obtained prior to the start of the study and informed consent (Appendix 1) was obtained from each patient before their clinical examination. An evaluation was carried out in the outpatient department where the patients were interviewed to collect data on demographic factors, presence of any habits, frequency and duration of the same etc (Appendix 2). Furthermore, clinical and histopathological examinations and blood investigations were performed to collect the required data for the study once approved by the institutional review board. Blood investigations included the estimation of serum lipid profile. The procedure for biochemical analysis and reagents used has been provided in appendix[3].

Data collected were entered in a Microsoft Excel sheet. Statistical analysis was performed using IBM SPSS version 24. Descriptive statistics of the baseline variables were first analysed. Mean and standard deviation was estimated for continuous variables whereas counts and percentages were calculated for nominal variables. The student's t-test was used to determine differences between the baseline variables. Mean values were compared by using one-way ANOVA to test the difference in lipid levels among the groups. In

the present study p <0.05 was considered the level of significance.

Results

Among the 60 selected patients for the current study, 46(76.67%) were males and 14(23.33%) were females. Ten patients were below 30 years of age and seven patients were more than 60 years of age and 43 patients were between 30 and 60 years of age. Among the 20 subjects in Group I, 10 had Leukoplakia, whereas the remaining 10 subjects had Erythroplakia. Similarly, in Group II, 10 individuals had Oral sub-mucous fibrosis and the remaining 10 patients had Oral LP. Baseline analysis revealed that there was no significant difference in the distribution of the population with regard to gender and age (Table 1).

Table 1: Baseline Characteristics

Characteristics		n	%	P-Value
Gender	Males	46	76.67	0.71
	Females	14	23.33	
Age	Less than 30	10	16.7	0.55
	30 to 40	17		
	41 to 50	16		
	51 to 60	10		
	More than 60	7		
Group I	Leukoplakia	10	50	
	Erythroplakia	10	50	
Group II	Oral sub-mucous fibrosis	10	50	
	Oral lichen planus	10	50	

In the comparison of serum lipid levels within the three study groups, the following results were obtained. The results comparing the serum lipid levels among the three groups have been summarised in table 2.

Total Cholesterol (TC)

From the results of total cholesterol estimation, it was found that the mean TC levels of group I, group II, and group III were 172.08 mg/dl, 171.43 mg/dl, and 179.15 mg/dl respectively.

No significant difference was observed while comparing the mean TC levels between the patients of group I and group II (p value>0.05). However, the mean TC level of group III having healthy individuals (control group) was found to be significantly higher than that of group I and group II (p value<0.05).

Total Glyceride (TG)

The results showed that the mean TG levels among group I, group II, and group III were 149.05mg/dl, 199.05mg/dl and 113.26mg/dl respectively. There was a significant difference observed while comparing the mean TG levels between the group I and group II patients (p value<0.05). Additionally, the mean TG level of the healthy control group was found to be significantly higher than that of group I and group II (p value<0.05).

HDL (High-Density Lipoprotein)

The mean HDL levels among the patients of the premalignant lesion, premalignant condition and control group were found to be 45.81 mg/dL, 46.57 mg/dL and 41.83 mg/dL respectively. Mean HDL levels of Group I did not differ significantly in comparison to Group II. However, group III having healthy individuals was found to be significantly less than that of group I and group II (p value<0.05).

LDL (Low-Density Lipoprotein)

From the study results, the mean LDL levels among subjects of premalignant lesion group, premalignant condition group and control group were found to be 96.46 mg/dL, 85.06 mg/dL and 114.67 mg/dL respectively. Significant results were obtained while

comparing the mean LDL levels among the three study groups (p value<0.05).

VLDL (Very Low-Density Lipoprotein)

The mean VLDL levels among the subjects of the study groups- premalignant lesion group, premalignant condition group and control group were found to be 29.81 mg/dL, 39.81 mg/dL and 22.65 mg/dL respectively. However, significant results were obtained while comparing the mean VLDL levels in between the study groups (p value<0.05).

Serum lipid profile	Descriptive Statistics			Test of significance		
	Group I	Group II	Group III	Group I vs GroupII	Group I vs III	Group II vs III
	Mean (SD)	Mean (SD)	Mean (SD)	P value	P value	P value
TC (mg/dL)	172.08(18.77)	171.43(9.28)	179.15(7.6)	0.44	0.0*	0.01*
HDL (mg/dL)	45.81(13.77)	46.57(12.14)	41.83(4.05)	0.12	0.04*	0.03*
TG (mg/dL)	149.05(49.9)	199.05(53.81)	113.26(7.53)	0.00*	0.01*	0.00*
LDL (mg/dL)	96.46(12.35)	85.06(46.92)	114.67(8.28)	0.04*	0.01*	0.01*
VLDL (mg/dL)	29.81(9.38)	39.81(45.64)	22.65(1.51)	0.04*	0.02*	0.01*

TC = HDL= High-Density Lipoprotein. TG = Triglyceride. LDL = Low-Density Lipoprotein. VLDL = Very High-Density Lipoprotein. Mg/dl = Miligram per deciliter. SD = Standard Deviation. * = Significant

Discussion

Assessment of serum lipid profile in patients with oral premalignant lesions was done in the study. A total of 60 subjects were enrolled out of which 20 were used as healthy control and out of the other 40; 20 patients were of oral premalignant conditions. This study had a greater proportion of male participants which is in concordance with studies conducted by Mehta R., et. al. and Garg D et. al. which included 85.7% and 75% male participants respectively [10,16]. The majority of participants in the three groups were between 30 to 50 years of age similar to the distribution reported by Gupta S., et. al. and Singh S., et. al. [17,18].

Although no significant differences were noted between groups I and II, the mean TC levels were prominently higher in the control group compared to the two pre-cancerous groups. Past studies conducted by Swamy MK., et. al., Garg D., et. al. and Mehta R., et. al. [10,19,16] reported a statistically significant decrease of plasma TC level is observed in the precancerous groups as compared to the control group similar to this study. However, Gupta S., et. al. reported a non-significant difference [17]. Low levels of cholesterol in the proliferating tissues and blood compartments could be due to the ongoing process of oncogenesis [6]. Three main hypotheses to explain the inverse relation between cholesterol concentrations and incidence of cancer 1) lower cholesterol levels before the carcinoma becomes symptomatic could be due to the ongoing cancer process 2) lower cholesterol levels serve as a biological marker for various other diseases even before being associated with carcinoma 3) cholesterol levels may be causally associated with other forms of cancer. Trans fatty acids increase membrane permeability to carcinogens is a mechanism for lower levels of cholesterols in malignancies.

In this study, the HDL level of the control group was significantly less than both the premalignant lesion and premalignant condition groups. These results were supported by past research by Garg D., et. al., Rawson K., et. al., Arias-Santiago S., et. al. and Aniyan KY., et. al. [10,20-22] which reported significantly lower levels of HDL among participants with premalignant conditions or lesions.

Mean TG levels of the premalignant lesion group were found to be significantly less compared to the premalignant condition group. Both these groups were

significantly higher than the control group. Goel P., et. al. found the TG levels were the highest among premalignant lesions, followed by premalignant conditions and finally among healthy controls. On the contrary, Mehta R., et. al. and Garg D., et. al. reported significantly lower levels of TG in precancerous groups compared to healthy controls [10,23]. Moreover, Subbulakshmi AC., et. al. did not observe any significant differences [16]. As seen above, there remains conflicting evidence about the level of serum TG among the group as noticed among studies. Tobacco carcinogens cause lipid peroxidation of the cell membrane and also during carcinogenesis formation of a new membrane occurs which utilises lipid particles in turn decreasing triglyceride levels [6].

A decrease in the mean serum LDL levels was observed in the precancerous groups as compared to the control group. These results were supported by past research by Subbulakshmi AC., et. al., Mujoo S., et. al. and Mehta R et. al. [16, 23, 24] which reported significantly lower levels among participants with premalignant conditions or lesions compared to healthy controls.

Plasma VLDL levels were significantly lower among precancerous groups as compared to the control group. Mehta R., et. al. reported similar findings [16] whereas Goel P., et. al. reported higher levels among premalignant lesion and condition groups in comparison to healthy controls [25].

Other than the above-mentioned mechanisms of the variation of serum lipid profile between precancerous groups and healthy controls are newly forming malignant cells require abnormally increase the number of lipids resulting in a decrease in storage, carcinoma may be associated with hypolipidemia, or also due to anti-oxidant vitamin therapy. Lipid peroxidation has a valuable role in cancer development as lipid peroxidation product, malondialdehyde, may cross-link deoxyribonucleic acid adenine and the required frequency of habit which can represent the status and the patients in the precancer group in our study, as a group, might represent patients who are in the initial stages of precancer, which might not have caused the lipid changes in the blood.

Conclusion

This observational research was conducted among a group of people in the Cossipore area in Kolkata, West Bengal for the evaluation and comparison of serum lipid levels in oral premalignant lesions and conditions. Written consent was taken from the patients prior to clinical examination, histopathological investigations (biopsy) and blood investigations. The study determined that mean values of all components of serum lipid profile investigation were significantly increased or decreased in the precancerous groups compared to healthy controls. Although the evidence was conflicting, our literature review helped us conclude that there was an agreement on the mean TC, HDL and LDL level changes in the precancerous group. In conclusion changes in lipid profile were found in oral premalignant disorders which can be used for early detection of carcinoma that can surge the survival rate because of early diagnosis and treatment as a potential biological marker for malignant transformation of oral premalignancy. A larger sample size is needed to make the test an efficient prognostic tool in life-threatening conditions.

Abbreviations

WHO- World Health Organization

OSMF- Oral submucous fibrosis

LP- Lichen planus

ANOVA- Analysis of variance

TC- Total Cholesterol

TG- Total Glyceride

HDL- High Density Lipoprotein

LDL- Low-Density Lipoprotein

VLDL- Very Low-Density Lipoprotein

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