RESEARCH ARTICLE

Exploratory Study to Evaluate Changes in Serum Lipid Levels as Early Diagnostic and/or Prognostic Indicators for Oral Submucous Fibrosis and Cancer among *Gutkha* Consumers in India

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Abstract

Background: In India smokeless tobacco users account for 25.9% of total tobacco use, Gutkha being the most common form. This study evaluated the association between serum lipid profile and Gutkha use as an early diagnostic and/or prognostic indicator for oral submucous fibrosis (OSMF) and oral cancer (Oral Ca) in non-smokers and non-alcohol consumers. Materials and Methods: A total of 163 participants were recruited from two sites in India. Participants were divided into four groups: individuals without any Gutkha chewing habit and without any oral lesions (control group), individuals with Gutkha chewing habit but without any oral lesions (GWL), patients with a confirmed clinical diagnosis of OSMF, and patients with a confirmed diagnosis of Oral Ca. Mixed linear modelling (MLM) was conducted to detect the change in mean serum lipid levels among four groups. Results: The sample consisted of 69% males and 31% females. Results of MLM show an inverse relationship between serum lipid levels in OSMF, and Oral Ca groups when compared to the control group. Conclusions: The results of our study demonstrated that GWL, OSMF and Oral Ca patients had lower serum lipid levels. Low serum lipid levels could be an indicator of initial neoplastic changes in oral cancer.

Keywords: Oral cancer - oral submucous fibrosis - gutkha - serum lipid levels

Asian Pac J Cancer Prev, **16 (15)**, 6439-6444

Introduction

Malignancies of the head and neck involve a diverse grouping of tumors with different histologic and anatomic variations. Tobacco use, mainly active or passive smoking and smokeless consumption is the most common cause for head and neck cancers (HNCs) (Chaturvedi, 2014; Combes and Franceschi, 2014; Dal Maso et al., 2015). According to the WHO, globally 21% of people aged ≥15 years smoked tobacco in 2012 (WHO, 2015). In India, prevalence of use of tobacco products is greater than that of global rates with 34.6% of people using some form of tobacco products during their lifetime. Of these, smokeless tobacco users accounted for 25.9% (WHO, 2010).

One of the most commonly used form of smokeless tobacco in India is in the form of Gutkha. Gutkha is a sweet flavored dry mixture of areca nut, tobacco with slaked lime and catechu (Patel et al., 2004). Gutkha is highly carcinogenic due to its components. Major carcinogens in Gutkha are tobacco-specific nitrosamines (N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and areca nut-specific nitrosamines (3-(methylnitrosamino) propionitrile) (Patel et al., 2004). Studies have suggested that constituents of Gutkha could release high levels of reactive oxygen species causing peroxidation of fatty acids. This is one of the several mechanisms for carcinogenesis. Increased levels of peroxidation of fatty acids could lead to increased utilization of lipids, which could be derived directly from blood or through the degradation of Expand HDL, LDL and VLDL very low density lipoprotein (VLDL), high density lipoprotein (HDL) and low density lipoprotein (LDL) (Ames, 1983; Patel et al., 2004).

There are several studies which looked at the effects of several tobacco products and serum lipid levels (Patel et al., 2004; Mehrotra et al., 2009; Goel et al., 2014; Mehta et al., 2014; Neerupakam et al., 2014; Poorey and Thakur, 2015). However, many of these studies did not control for adjuvant use of smoking and alcohol use which are established risk factors for developing oral cancers (Aruna et al., 2011; Anantharaman et al., 2014; Krishna et al., 2014). The aim of this study was to evaluate the association between serum lipid profile and Gutkha use as an early diagnostic and/or prognostic indicator in oral submucous fibrosis (OSMF) and oral cancer (Oral Ca) patients who are non-smokers and non-alcoholics.

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Materials and Methods

Participants

The participants for this study were recruited between January 2012 and December 2013 from two sites in Bhopal, India: People's College of Dental Sciences and Research Centre (PCDSRC), and Jawaharlal Nehru Cancer Hospital (JNCH). All new patients coming to the outpatient department (OPD) during the recruitment period at these sites were informed about the study, and were told that the participation in this study was voluntary. Participants were given information about the study, and written informed consent was taken in local language before their enrollment. A total of 163 participants from PCDSRC, and 80 participants from JNCH were found eligible for the study (Figure. 1).

Inclusion and exclusion criteria

Male and female participants, who were between the ages of 18 to 80 years; with or without a history of Gutkha chewing habit were considered for this study. Included participants were further stratified by presence of any oral lesions or oral malignancies.

Participants who refused to consent; who were below the age of 18 years and above 80 years; regular smokers and alcohol users; individuals with severe mental or severe health conditions that could prohibit them from participating in the study; and patients who were already being treated for OSMF or Oral Ca were excluded from the study.

Estimation of serum lipid profile

Fasting blood samples were collected in blood collection tubes and were labelled with individual patient ID. Serum was extracted after centrifugation and stored at -10°C until analyses were done. Plasma levels of total cholesterol (TC), triglycerides (TG), very low density lipoprotein (VLDL), high density lipoprotein (HDL) and low density lipoprotein (LDL) were calculated by using Biosystem™ reagents and Autoanalyser™. Normal blood lipid levels were described as: TC: 75-169 mg/dL for those aged ≤20 years, and 100-199 mg/dL for those >20 years; HDL: >40 mg/dL; LDL: <130 mg/dL for individuals who were at low risk for coronary artery disease; and TG: <150 mg/dL (Cleveland Clinic, 2014).

Power and sample size

To detect a difference in means with effect size=0.40 (large effect) among four groups, a total sample size of

Table 1. Mean and standard deviation (SD) of participant's TC, TG, HDL, LDL, and VLDL levels (mg/dL), stratified by four groups

Characteristic	Group			
	Control	GWL	OSMF	Oral Ca
TC	194.4 (18.1)	183.2 (7.8)	167.9 (14.2)	160.4 (7.6)
TG	112.1 (22.7)	114.1 (4.8)	108.1 (9.2)	100.8 (5.3)
HDL	43.3 (5.8)	38.3 (3.2)	28.1 (6.4)	27.9 (2.7)
LDL	127.5 (15.9)	122.9 (7.9)	118.2 (14.3)	112.7 (7.3)
VLDL	22.3 (4.6)	22.8 (0.97)	21.6 (1.9)	20.2 (1.1)

TC - total cholesterol, TG - triglycerides, VLDL - very low density lipoprotein, HDL - high density lipoprotein, and LDL - low density lipoprotein

Table 2. Results from One-Way ANOVA analysis. Post-hoc Comparisons with Bonferroni Adjustment

Dependent variable	Group (I)	Group (J)	Mean Difference (I-J)	95% CI Lower	95% CI Upper	p-value
TC	Control	GWL	11.2	2	20.3	<0.01
		OSMF	26.5	17.4	35.7	<0.0001
		Oral Ca	34.1	24.9	43.2	<0.0001
TG	Control	GWL	-2.1	-12.5	8.4	> 0.05
		OSMF	4	-6.4	14.4	> 0.05
		Oral Ca	11.3	1	21.7	< 0.05
HDL	Control	GWL	4.9	1.7	8.1	<0.0001
		OSMF	15.2	11.9	18.4	<0.0001
		Oral Ca	15.4	12.2	18.6	<0.0001
LDL	Control	GWL	4.7	-3.7	13	> 0.05
		OSMF	9.4	1.1	17.7	< 0.05
		Oral Ca	14.8	6.5	23.1	<0.0001
VLDL	Control	GWL	-0.5	-2.6	1.6	> 0.05
		OSMF	0.7	-1.4	2.8	> 0.05
		Oral Ca	2.2	0.1	4.3	< 0.05

TC - total cholesterol, TG - triglycerides, VLDL - very low density lipoprotein, HDL - high density lipoprotein, and LDL - low density lipoprotein

Table 3. Mixed linear modelling for TC, TG, HDL, LDL, and VLDL

	Group	Estimate	95% CI		p-value
			Lower	Upper	
TC	Intercept	194.4	191.1	197.7	<0.0001
	Control	Ref.	–	–	–
	GWL	-11.2	-17.8	-4.5	<0.01
	OSMF	-26.5	-33.2	-19.9	> 0.05
	Oral Ca	-34.1	-40.7	-27.4	<0.0001
TG	Intercept	112.1	108.3	115.9	<0.0001
	Control	Ref.	–	–	–
	GWL	2.1	-5.5	9.6	> 0.05
	OSMF	-4	-11.6	3.6	> 0.05
	Oral Ca	-11.3	-18.9	-3.7	< 0.01
HDL	Intercept	43.3	42.1	44.4	<0.0001
	Control	Ref.	–	–	–
	GWL	-4.9	-7.3	-2.6	<0.0001
	OSMF	-15.2	-17.5	-12.8	<0.0001
	Oral Ca	-15.4	-17.7	-13.1	<0.0001
LDL	Intercept	127.5	124.5	130.6	<0.0001
	Control	Ref.	–	–	–
	GWL	-4.7	-10.7	1.4	> 0.05
	OSMF	-9.4	-15.4	-3.3	< 0.01
	Oral Ca	-14.8	-20.8	-8.7	<0.0001
VLDL	Intercept	22.3	21.6	23.1	<0.0001
	Control	Ref.	–	–	–
	GWL	0.5	-1	2	> 0.05
	OSMF	-0.7	-2.2	0.8	> 0.05
	Oral Ca	-2.2	-3.7	-0.6	< 0.01

Model was adjusted for age and gender; TC - total cholesterol, TG - triglycerides, VLDL - very low density lipoprotein, HDL - high density lipoprotein, and LDL - low density lipoprotein

76 participants was required to achieve a statistical power of 80% at 0.05 alpha.

Data collection and analysis

Information about patient's gender, age, socio economic status (SES), presence of any oral lesions, Gutkha chewing habit, oral cancer status, staging of the cancer, lymph node involvement, extent of the tumor, fasting blood lipid profile including TC, TG, HDL, LDL and VLDL levels were collected. Patient information was deidentified using patient ID numbers and patient data were entered into a data collection form developed using Epi Info software version 7.1.5 (CDC, 2014). All patient records and blood specimen samples were collected and stored in the Department of Oral Pathology at PCDSRC. Data from both study sites were merged and participants were divided into four groups: individuals without any Gutkha chewing habit and without any oral lesions (control group), individuals with Gutkha chewing habit but without any oral lesions (GWL), patients with a confirmed clinical diagnosis of oral submucous fibrosis (OSMF), and patients with a confirmed histological diagnosis of oral squamous cell carcinoma (Oral Ca) (Figure 1). All participants in the GWL, OSMF, and Oral Ca groups were regular Gutkha chewers (≥5 packets per day). None of the

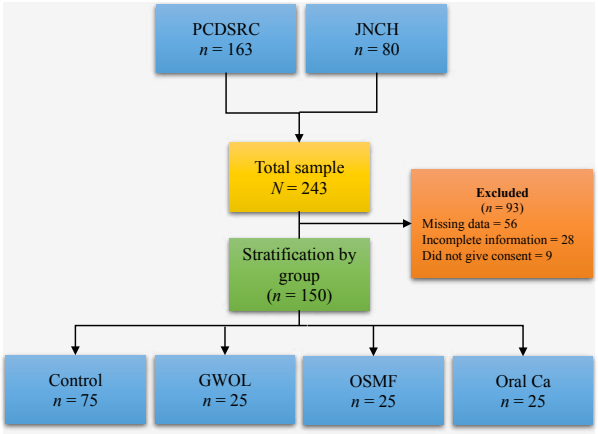

Figure 1. Flow chart of the process of participant selection and stratification

participants were smokers or drank alcohol. Data gathered by laboratory procedures were also matched and merged using patient ID.

Univariate analyses were performed for each variable. Percentage, means and standard deviation were calculated. For analyzing difference in means, one-way analysis of variance (ANOVA) and one-way nonparametric analysis were performed. Finally, mixed linear modelling (MLM) analysis, adjusting for age and gender were conducted to compare estimates for fasting blood lipid levels among all groups, with control group set as the reference category. Test for normality and outliers showed that the data from control and OSMF groups did not follow normal distribution for TC, TG, HDL, LDL, and VLDL levels. MLM analysis and non-parametric median analysis were performed to account for non-normality of the data. Associations were considered significant at $p < 0.05$. Data analysis was conducted using SAS® software version 9.3.

Results

Two hundred and forty three participants met the inclusion criteria. Of these, 93 participants were excluded due to lack of consent, missing data, and incomplete diagnostic information. The final analytical sample consisted of 150 participants with 69% males and 31% females (Males=104, Females=46) who were stratified into Control (n=75; M=43, F=32), GWL (n=25; M=22, F=3), OSMF (n=25; M=20, F=5) and Oral Ca (n=25; M=19, F=6) groups. The mean age of all the participants was 41.4 years (SD=15.0). The minimum and maximum age within the sample was 18 years and 78 years, respectively. Mean and standard deviation (SD) of participant's TC, HDL, LDL, VLDL, and TG levels, stratified by four groups are shown in Table 1. In general, participants in the control group had higher levels of TC, TG, HDL, LDL, and VLDL (Table 1). The only exception being GWL group, which had slightly higher mean VLDL and TG levels as compared to the control group. The results from One-Way ANOVA analysis with post-hoc comparisons using Bonferroni adjustment are described in Table 2. The control group had significantly higher levels of TC, and HDL as compared to the GWL, OSMF, and

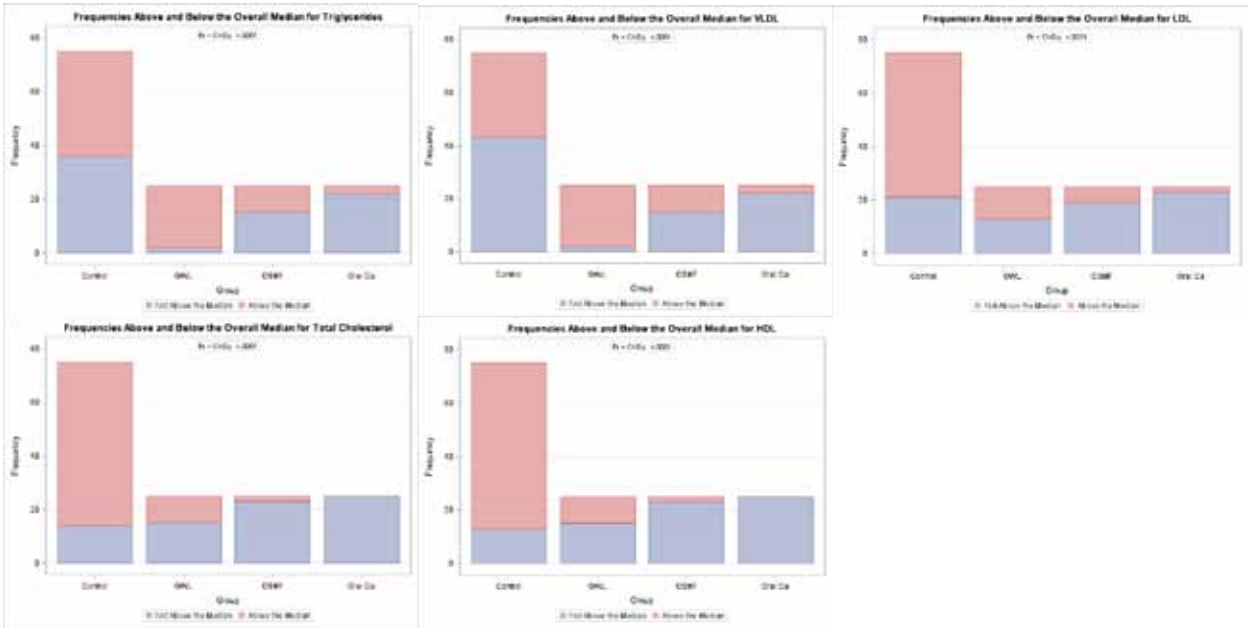

Figure 2. Median Plot for Response Variables by Groups. Median plot shows the frequencies above and below the overall median for TC, TG, HDL, LDL, and VLDL levels

Oral Ca groups (Table 2). Difference in mean LDL levels were only significant among Control, OSMF, and Oral Ca groups. For VLDL and TG levels, only control and Oral Ca groups showed significant differences in mean values.

Median plot for serum lipids by groups shows that most values for the control group fell above the overall median for TC, TG, HDL, LDL, and VLDL levels (Figure 2). Results of MLM analysis show an inverse relationship between serum lipid levels in OSMF, and Oral Ca groups when compared to the control group. For one unit increase in TC levels in control group, levels in GWL group were decreased by approximately 11 units ($p<0.01$) and by 34 units in Oral Ca group ($p<0.0001$). For one unit increase in TG levels in control group, levels in Oral Ca group showed a decrease of 11 units ($p<0.01$). For one unit increase in the control group, the HDL levels among GWL, OSMF and Oral Ca group showed a decrease of 5, 15, and 15 units respectively ($p<0.0001$). LDL was also found to decrease by 9 ($p<0.01$) and 15 units ($p<0.0001$) in OSMF and Oral Ca groups as compared to a one unit increase in the control group. For VLDL levels, only Oral Ca group showed a significant decrease of 2 units ($p<0.01$) when compared to a one unit increase in the control group. Estimates and 95% confidence intervals (95% CI) from MLM analysis are shown in Table 3.

Discussion

The results of our study confirms some of the findings from previous researches (Athirajan et al., 2014; Goel et al., 2014; Mehta et al., 2014; Neerupakam et al., 2014; Poorey and Thakur, 2015). Our study shows that the levels of fasting blood lipids are lower among people with OSMF and Oral Ca. In addition, the study also shows that fasting lipid levels are lower among regular Gutkha users which indirectly suggest that Gutkha chewing could be a risk factor for oral cancer. OSMF and Oral Ca are highly prevalent in India and other South Asian countries where levels of Gutkha and tobacco use is high (Gupta and Ray, 2003). Several studies have shown a direct epidemiological relationship between Gutkha use, OSMF and Oral Ca (Baskar et al., 2004; Nair et al., 2004; Patel et al., 2004; Mehrotra et al., 2009; Lohe et al., 2010; Chawda et al., 2011; Wiwanitkit and Wiwanitkit, 2011; Baig et al., 2012; Taqi, 2012; Sherubin et al., 2013; Singh et al., 2013; Srinivas et al., 2013; Bailwad et al., 2014; Garg et al., 2014; Goel et al., 2014; Mehta et al., 2014; Neerupakam et al., 2014; Poorey and Thakur, 2015) Results from this study, although indirectly, support these findings.

Lipids are important for normal functioning of cells. Normal levels of cholesterol is an important structural component of cell membranes. It is also involved in several enzymatic processes and genetic stability (Raffy and Teissie, 1999; Patel et al., 2004). Higher levels of cholesterol can lead to several diseases including myocardial infarction (Gordon et al., 1989). But, the implications of lower levels of cholesterol in the body is uncertain. Reduced levels of blood lipid levels have been shown to be associated with several cancers like acute lympoblastic leukemia, myelodysplastic syndromes, and solid organ cancers like esophageal cancers and head and neck cancers (Budd and Ginsberg, 1986; Chyou et al., 1992; Halton et al., 1998; Patel et al., 2004; Strohmaier et al., 2013; Goyal et al., 2014). Cholesterol has also been linked to mortality rates in cancer patients (Strohmaier et al., 2013). For example, in a secondary analysis among 7,718 men between 40 to 64 years age, decreased plasma cholesterol levels was associated with 66% higher mortality rate (Rose and Shipley, 1980). There are several hypotheses for lower cholesterol levels in cancer patients. One of the earlier hypotheses was proposed by Kark et al. (1982). According to Kark et al. (1982) lower levels of cholesterol among cancer patients could be due to the cancer process itself; or due to the effects of carcinogenic

etiological factors; or the lower levels of cholesterol is only seen in some forms of cancers only. Another reason for lower lipid levels in oral cancer patients could be due to the fact that oral lesions interferes with food intake. In addition, hormonal levels and genetic factors could also be associated with plasma cholesterol levels. The role of hormones and genetic factors could be better understood by reviewing lipoprotein transport system (Brown et al., 1981; Williams et al., 1992). An important constituent of lipoprotein transport system is the receptors for lipoproteins in liver and other organs like adipose tissue (Brown et al., 1981). These receptors help in the uptake of circulating lipoproteins like chylomicrons, VLDL, LDL and HDL into the cell where it is degraded to release the cholesterol. Hence, the plasma cholesterol level is influenced by several factors like amount ingested, rate of in vivo synthesis, efficacy of lipoprotein receptors and its catabolism. Of these factors, the most important one is LDL receptors which help the uptake of LDL, the main protein which transport cholesterol into the cells (Brown et al., 1981).

The major finding of our study was that TC, TG, HDL, LDL, and VLDL were lower among people with oral cancer group compared to control group. Similarly, HDL, and LDL levels were lower among patients with OSMF. Many previous studies support these results (Budd and Ginsberg, 1986; Patel et al., 2004; Mehrotra et al., 2009; Wiwanitkit and Wiwanitkit, 2011; Sherubin et al., 2013; Singh et al., 2013; Bailwad et al., 2014; Garg et al., 2014; Goel et al., 2014; Mehta et al., 2014; Poorey and Thakur, 2015). Several studies have shown that, in malignant conditions, low levels of cholesterol in proliferating tissues and blood are due to carcinogenesis. It is not well established whether it is a cause of cancer or an effect of it. However, normalization of plasma cholesterol level in patients treated with chemotherapy suggest that it is the tumor burden that is related to low cholesterol level, and not that people with low cholesterol level is at risk to develop cancer. Previous studies have shown that low plasma levels of HDL is a predictor of cancer (Budd and Ginsberg, 1986; Patel et al., 2004). This was attributed to the use by cholesterol in membrane synthesis. Similar to our results, previous studies have also shown decrease in serum triglyceride level in cancer patients as well (Mehrotra et al., 2009).

The TG and VLDL levels showed an increase in GWL compared to control group, although the results were statistically non-significant. Similarly, decrease in TG and VLDL levels between OSMF and control group was non-significant. These non-significant decrease in lipid levels could be due to the fact that the participants in the comparison groups, GWL and OSMF, are at the early stages of the cancer.

Strengths and limitations

Given exploratory nature of this study, inclusion of patients from two sites without proper randomization was a limitation. The association of Gutkha exposure with OSMF or Oral Ca could be weaker because of this selection bias. However, we nearly doubled our sample size and the total OPD patients who came to these two hospitals during the study period were a good representation of the general population. Strengths of our study include the exclusion of participants who were smokers or consumed alcohol. Smoking and alcohol are well known causative agents for oral cancers (Anantharaman et al., 2014) and by excluding such patients, we controlled for known confounding variables. Another strength of our study was that although exploratory, we used a control group for comparison and a large sample size thus increasing the power and internal validity to test our hypothesis.

The results of our study demonstrated that OSMF and oral cancer patients had lower serum lipid levels. Low serum fasting lipid levels were also seen among those participants who were Gutkha users but did not have any oral lesions. Low serum fasting lipid levels could be considered as an indicator of the initial neoplastic changes in oral cancer. Future studies should explore the relationships between different histological grading and stages of oral cancer and serum fasting lipid levels longitudinally.

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