ISSN (O): 2582-693X

Original Article

EFFECT OF SMOKING ON BLOOD PARAMETERS: COMPARATIVE STUDY BETWEEN PATIENTS HAVING MELANOSIS AND NORMAL MUCOSA

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ABSTRACT

Introduction - There are more than one billion smokers in the world with an increased habit of smoking worldwide more than three million people currently die each year from smoking. Young people are smoking earlier and more heavily.

Material and methods_ The study was carried out in the Postgraduate Department of Oral Pathology and microbiology, Daswani Dental College and Research Centre, Kota. Patients with potentially malignant oral lesions (PMOD) with history of tobacco habit for a minimum of consecutive 5 years and patients with history of tobacco habit for a minimum of consecutive 5 years but without any potentially malignant oral lesions(PMOD) were selected for the study. Total 100 (50+50) subjects were selected.

Results:Comparing the mean total cholesterol of two groups, t test showed significantly different and lower (15.4%) TC in Group II as compared to Group I (172.41 ± 4.86 vs. 145.80 ± 2.36, t=4.92, p<0.001).

Conclusion - Prospective studies on a large sample of tobacco abusers followed up for a long duration will help in proving or disproving the role of metabolic derangement in oral carcinogenesis.

Keywords :Smoking, total cholesterol, high density lipoprotein, low density lipoprotein, very low density lipoprotein, HbA1c, blood glucose.

INTRODUCTION

There are more than one billion smokers in the world with an increased habit of smoking worldwide more than three million people currently die each year from smoking. In a study by World

Health Organization, the gender empowerment measure has been shown to be positively and significantly correlated to gender smoking ratio. About one billion men and 250 million women are daily smokers worldwide. But in India, tobacco consumption continues to rise, even though the evidence mount regarding its hazards. Young people are smoking earlier and more heavily.

AIMS AND OBJECTIVES

- To assess the association between anemia, hyperglycemia, and hyperlipidemia with development of potentially malignant oral lesions in tobacco users.
- Hence compare serum parameters between the tobacco users with PMOD and tobacco users without PMOD.

MATERIAL AND METHODS

The study was carried out in the Postgraduate Department of Oral Pathology and microbiology, Daswani Dental College and Research Centre, Kota, Rajasthan. Patients with potentially malignant oral lesions (PMOD) with history of tobacco habit for a minimum of consecutive 5 years and patients with history of tobacco habit for a minimum of consecutive 5 years but without any potentially malignant oral lesions (PMOD) were selected for the study. Total 100 (50+50) subjects were selected. Patients diagnosed with any other systemic disorders except hyperlipidemia, hyperglycemia, and iron deficiency anemia were excluded from the study.

4ml of venous blood was withdrawn from antecuboital fossa of left arm under asceptic condition. Sample taken was immediately transferred into a glass vial containing EDTA. Serum Hemoglobin, Serum Lipid Profile, Serum Glycosylated Hemoglobin was assessed using the following methods. The results obtained was compared and correlated statistically to assess the possible association between selected serum markers and PMODs.

Data were summarized as Mean ± SE (standard error of the mean). Groups were compared by independent Student's t test. Categorical (discrete) groups were compared by chi-square (χ^2) test. A two-tailed (α=2) p value less than 0.05 ($p<0.05$) was considered statistically significant. Analyses were performed on SPSS (windows version 17.0).

OBSERVATIONS AND RESULTS

The present study compares the selected blood parameters among tobacco users with and without potentially malignant oral disorders. Total 100

DOI: 10.46376/IJMR/2.3.2021.

subjects were recruited, 50 tobacco users without potentially malignant oral disorders (Group I) and 50 tobacco users with potentially malignant oral disorders (Group II). The outcome measures of the study were TC, HDLC, LDL, VLDL, TG, HbA1c, MBG and Hb. All blood parameters were measured in mg/dl except HbA1c which is measured in %. The objective of the study was to compare the blood parameters between the two groups (Group I and Group II).

DEMOGRAPHIC CHARACTERISTICS

The demographic characteristics of two groups are summarized in Table 1. The age of Group I and Group II ranged from 17 to 70 yrs and 19 to 72 yrs respectively with mean (± SE) 36.60 ± 1.65 yrs and 38.98 ± 1.42 yrs respectively and median 35 yrs and 40 yrs respectively. Further, in both groups, there were 11 (22.0%) females and 39 (78.0%) males and thus the sex proportion (F/M) was also similar between the two groups (χ^2=0.00, p=1.000).

Similarly, the type of habit (χ^2=4.38, p=0.223) and duration of habit (χ^2=1.98, p=0.159) also not differed between the two groups i.e. found to be statically the same. In other words, subjects of two groups were demographically matched and comparable and thus may also not influence the study outcome measures (i.e. blood parameter levels).

Table 1: Demographic characteristics of two groups

Demographic Characteristics	Group I (n=50)	Group II (n=50)	t/χ^2 value	p value
Age (yrs): Mean ± SE	36.60 ± 1.65	38.98 ± 1.42	1.09	0.277
Sex: Female Male	11 (22.0) 39 (78.0)	11 (22.0) 39 (78.0)	0.00	1.000
Type of habit: Tobacco chewer Tobacco chewer & smoker Tobacco chewer & alcohol Tobacco chewer, smoker & alcohol	30 (60.0) 10 (20.0) 8 (16.0) 2 (4.0)	24 (48.0) 9 (18.0) 9 (18.0) 8 (16.0	4.38	0.223
Duration of habit (yrs): ≤ 10 > 10	26 (52.0) 24 (48.0)	19 (38.0) 31 (62.0)	1.98	0.159
Demographic characteristics	**Group I (n=50)**	**Group II (n=50)**	**t/χ^2 value**	**p value**
Age (yrs): Mean ± SE	36.60 ± 1.65	38.98 ± 1.42	1.09	0.277
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Type of habit: Tobacco chewer Tobacco chewer & smoker Tobacco chewer & alcohol Tobacco chewer, smoker & alcohol	30 (60.0) 10 (20.0) 8 (16.0) 2 (4.0)	24 (48.0) 9 (18.0) 9 (18.0) 8 (16.0)	4.38	0.223
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Table 1: Demographic characteristics of two groups

Outcome measures

I. Total Cholesterol (TC)

The TC of two groups is summarized in Table 2. The TC of Group I and Group II ranged from 102.5 to 240.0 mg/dl and 82.0 to 193.0 mg/dl with mean (± SE) 172.41 ± 4.86 mg/dl and 145.80 ± 2.36 mg/dl respectively and median 171 mg/dl and 144 mg/dl respectively. The mean TC lowered comparatively in Group II as compared to Group I. Comparing the mean TC of two groups, t test showed significantly different and lower (15.4%) TC in Group II as compared to Group I (172.41 ± 4.86 vs. 145.80 ± 2.36, t=4.92, p<0.001).

Table 2: TC (Mean ± SE) of two groups

Group I (n=50)	Group II (n=50)	t value	p value
172.41 ± 4.86 (102.5 to 240.0)	145.80 ± 2.36 (82.0 to 193.0)	4.92	<0.001

Numbers in parenthesis indicates the range (min to max)

II. High Density Lipoprotein Cholesterol (HDLC)

The HDLC of two groups is summarized in Table 3. The HDLC of Group I and Group II ranged from 34.2 to 70.0 mg/dl and 21.8 to 64.3 mg/dl with mean (± SE) 53.99 ± 1.34 mg/dl and 45.06 ± 1.20 mg/dl respectively and median 54 mg/dl and 47 mg/dl respectively. The mean HDLC lowered comparatively in Group II as compared to Group I. Comparing the mean HDLC of two groups, t test showed significantly different and lower (16.6%) HDLC in Group II as compared to Group I (53.99 ± 1.34 vs. 45.06 ± 1.20, t=4.97, p<0.001).

Table 3: HDLC (Mean ± SE) of two groups

Group I (n=50)	Group II (n=50)	t value	p value
53.99 ± 1.34 (34.2 to 70.0)	45.06 ± 1.20 (21.8 to 64.3)	4.97	<0.001

Numbers in parenthesis indicates the range (min to max)

III. Low Density Lipoprotein Cholesterol (LDL)

The LDL of two groups is summarized in Table 4. The LDL of Group I and Group II ranged from 29.1 to 121.7 mg/dl and 30.4 to 106.1 mg/dl with mean (± SE) 86.07 ± 2.94 mg/dl and 76.86 ± 1.67 mg/dl respectively and median 84 mg/dl and 78 mg/dl respectively. The mean LDL lowered comparatively in Group II as compared to Group I. Comparing the mean LDL

DOI: 10.46376/IJMR/2.3.2021.

of two groups, t test showed significantly different and lower (10.7%) LDL in Group II as compared to Group I (86.07 ± 2.94 vs. 76.86 ± 1.67, t=2.72, p=0.008).

Table 4: LDL (Mean ± SE) of two groups

Group I (n=50)	Group II (n=50)	t value	p value
86.07 ± 2.94 (29.1 to 121.7)	76.86 ± 1.67 (30.4 to 106.1)	2.72	0.008

Numbers in parenthesis indicates the range (min to max)

IV. Very Low Density Lipoprotein Cholesterol

The VLDL of two groups is summarized in Table 5. The VLDL of Group I and Group II ranged from 17.8 to 52.7 mg/dl and 6.1 to 45.0 mg/dl with mean (± SE) 32.79 ± 1.49 mg/dl and 23.63 ± 0.92 mg/dl respectively and median 31 mg/dl and 23 mg/dl respectively. The mean VLDL lowered comparatively in Group II as compared to Group I. Comparing the mean VLDL of two groups, t test showed significantly different and lower (27.9%) VLDL in Group II as compared to Group I (32.79 ± 1.49 vs. 23.63 ± 0.92, t=5.23, p<0.001).

Table 5: VLDL (Mean ± SE) of two groups

Group I (n=50)	Group II (n=50)	t value	p value
32.79 ± 1.49 (17.8 to 52.7)	23.63 ± 0.92 (6.1 to 45.0)	5.23	<0.001

Numbers in parenthesis indicates the range (min to max)

V. Total TriGlycerides

The TG of two groups is summarized in Table 6 and also shown in Graph. 9. The TG of Group I and Group II ranged from 89.0 to 263.6 mg/dl and 30.3 to 225.0 mg/dl with mean (± SE) 163.94 ± 7.45 mg/dl and 118.15 ± 4.60 mg/dl respectively and median 157 mg/dl and 114 mg/dl respectively. The mean TG lowered comparatively in Group II as compared to Group I. Comparing the mean TG of two groups, t test showed significantly different and lower (27.9%) TG in Group II as compared to Group I (163.94 ± 7.45 vs. 118.15 ± 4.60, t=5.23, p<0.001).

Table 6: TG (Mean ± SE) of two groups

Group I (n=50)	Group II (n=50)	t value	p value
163.94 ± 7.45 (89.0 to 263.6)	118.15 ± 4.60 (30.3 to 225.0)	5.23	<0.001

Numbers in parenthesis indicates the range (min to max)

DOI: 10.46376/IJMR/2.3.2021.

VI. Hemoglobin A1c (HbA1c)

The HbA1c of two groups is summarized in Table 7. The HbA1c of Group I and Group II ranged from 4.2 to 6.3% and 4.2 to 6.5% with mean (± SE) 5.46 ± 0.07% and 5.27 ± 0.07% respectively and median 6% and 5% respectively. The mean HbA1c lowered slightly in Group II as compared to Group I. Comparing the mean HbA1c of two groups, t test showed similar HbA1c between two groups (5.46 ± 0.07 vs. 5.27 ± 0.07, t=1.83, p=0.070) though it lower 3.5% in Group II as compared to Group I.

Table 7: HbA1c (Mean ± SE) of two groups

Group I (n=50)	Group II (n=50)	t value	p value
5.46 ± 0.07 (4.2 to 6.3)	5.27 ± 0.07 (4.2 to 6.5)	1.83	0.070

VII. Mean Blood Glucose (MBG)

The MBG of two groups is summarized in Table 8. The MBG of Group I and Group II ranged from 43.0 to 128.0 mg/dl and 43.0 to 138.0 mg/dl with mean (± SE) 88.82 ± 3.19 mg/dl and 80.30 ± 3.40 mg/dl respectively and median 94 mg/dl and 76 mg/dl respectively. The mean MBG lowered slightly in Group II as compared to Group I. Comparing the mean MBG of two groups, t test showed similar MBG between two groups (88.82 ± 3.19 vs. 80.30 ± 3.40, t=1.83, p=0.071) though it lower 9.6% in Group II as compared to Group I.

Table 8: MBG (Mean ± SE) of two groups

Group I (n=50)	Group II (n=50)	t value	p value
88.82 ± 3.19 (43.0 to 128.0)	80.30 ± 3.40 (43.0 to 138.0)	1.83	0.071

Numbers in parenthesis indicates the range (min to max)

VIII. Hb

The Hb of two groups is summarized in Table 9. The Hb of Group I and Group II ranged from 10.4 to 14.0 mg/dl and 10.6 to 14.4 mg/dl with mean (± SE) 12.93 ± 0.12 mg/dl and 12.61 ± 0.11 mg/dl respectively and median 13 mg/dl and 13 mg/dl respectively. The mean Hb lowered slightly in Group II as compared to Group I. Comparing the mean HB of two groups, t test showed similar Hb between two groups (12.93 ± 0.12 vs. 12.61 ± 0.11, t=1.95, p=0.054) though it lower 2.5% in Group II as compared to Group I.

DOI: 10.46376/IJMR/2.3.2021.

Table 9: Hb (Mean ± SE) of two groups

Group I (n=50)	Group II (n=50)	t value	p value
12.93 ± 0.12 (10.4 to 14.0)	12.61 ± 0.11 (10.6 to 14.4)	1.95	0.054

Numbers in parenthesis indicates the range (min to max)

DISCUSSION

The present study was undertaken in Daswani dental college and research centre, Kota, Rajasthan. It compares selected blood parameters among tobacco users with and without potentially malignant oral disorders. A total of 100 subjects were recruited, 50 tobacco users without potentially malignant oral disorders (Group I) and 50 tobacco users with potentially malignant oral disorders (Group II). The outcome measures of the study were TC, HDLC, LDL, VLDL, TG, HbA1c, MBG and Hb. All blood parameters were measured in mg/dl except HbA1c which is measured in %. The objective of the study was to compare the blood parameters between the two groups (Group I and Group II).

The results of the study showed that mean Total Cholesterol (TC), mean High Density Lipoprotein Cholesterol (HDLC), mean Low Density Lipoprotein Cholesterol (LDL), mean Very Low Density Lipoprotein Cholesterol (VLDL) and mean Total Triglycerides (TG) were significantly lowered ($p<0.001$) in Group II (tobacco users with potentially malignant oral disorders) as compared to Group I (tobacco users without potentially malignant oral disorders). There was also a slight decrease in the mean Hemoglobin A1c (HbA1c) and mean blood glucose (MBG) in Group II but these differences were statistically not significant ($p=0.070$) and ($p=0.071$). Similarly the mean Hemoglobin (Hb) was slightly lowered in Group II as compared to Group I but the difference was not statistically significant ($p=0.054$).

In the present study the values evidently show that Precancer and Oral Cancer patients have lower serum cholesterol, significantly lower serum HDL cholesterol and lower serum triglyceride values when compared with healthy control groups. These results are consistent with the result of studies by **Lohe et al in 2010** who found that significant decrease in TC, HDL, VLDL, and triglyceride in Oral Cancer group; and significant decrease in TC, and HDL in

DOI: 10.46376/IJMR/2.3.2021.

Oral precancer group as compared to Control[1]

Gaurav Ghosh et al in 2011 also found similar results in their study; there was significant decrease in TC, HDL, VLDL, and triglyceride in Oral Cancer group; and significant decrease in TC, and HDL in Oral precancer group as compared to Control[2]

Result was also consistent with the study of **P S Patel et al. in 2004.** They found a significant decrease in plasma total cholesterol and HDLC in patients with oral cancer as compared to control[3] Result was also consistent with the study of **Shally Gupta et al. in 2011** who found that a significant decrease in HDLC and triglyceride in oral squamous cell carcinoma patients as compared to the controls[4] Result was also consistent with the study of **Pathan A B et al. in 2012** who found that a significant decrease in plasma lipid profile in oral cancer patients as compared to the controls[5] Result was also consistent with the study of **Jyoti G Chawda et al. in 2011** who found that a significant decrease in serum cholesterol, HDL & TGs in oral cancer patients as compared to the controls.[6]

In the present study the values evidently show that OMSF patients have significantly lower serum cholesterol, lower serum HDL cholesterol and lower serum triglyceride values when compared with healthy control groups. This result is consistent with the study of **Syeda Arshiya Ara** et al. in 2013 who had reported the parameters of lipid profile for the OSMF group showed a significant decrease when compared to normal subjects. She reported that 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 [7].

Ravi Mehrotra et al. in 2009 observed that a significant decrease in plasma total cholesterol, HDLC and Apo-A1 in patients with OSMF as compared to the controls. Thus an inverse relationship between plasma lipid levels and patients was found in OSMF [8]. Results were also consistent with the study of **Altaf Hussain Chalkoo et al in 2011**. They reported a significant decrease in Serum cholesterol and LDLC whereas serum triglycerides and HDLC were slightly increased in some patients with OSMF. Thus, study

DOI: 10.46376/IJMR/2.3.2021.

strengthens the evidence of alterations in plasma lipid levels in OSMF patients [9] Result was also consistent with the study of **Pramod kumar et al. in 2013.**They found that a statistically significant decrease in plasma total cholesterol, LDL and HDL was observed in patients with OSMF as compared to the controls[10]. Result was also consistent with the study of **Gopal Sharma et al. in 2013.** They found a significant decrease in serum cholesterol, LDLC and LDLC/HDLC ratio in OSMF patients [11].

This may be due to tobacco carcinogenesis which induce generation of free radicals and reactive species, which are responsible for high rate of oxidation / peroxidation of polyunsaturated fatty acids. Another hypothesis says that hypolipidemia is a result of direct lipid lowering effect of tumor cells as these neoplastic cells directly utilize cholesterol for their own metabolism, thus it can be stated that the lower serum lipid status may be a useful indicator i.e, biochemical marker for initial changes occurring in neoplastic cells [12].

Only few research studies have been done on diabetes and oral cancer. The molecular mechanisms associated with diabetes and cancer development are still not clear. The association between diabetes and oral cancers may be due to shared risk factors between the two diseases, such as diet, aging, obesity and physical inactivity. However, the etiologic factors of oral cancer such as tobacco, alcohol can also contribute to oral cancer in diabetic patients. Hyperglycemia generates oxidative stress that damages the DNA and induces carcinogenesis. Hyperinsulinemia is the characteristic feature of diabetes Type II patients. Insulin activates the structurally similar insulin-like receptor that increases the risk of cancer. Hyperinsulinemia causes unregulated insulin receptor signaling that increases cancer risk by its proliferative and antiapoptotic effects. It also causes increased mitogenic activity of insulin post-receptor molecular mechanisms like intracellular up-regulation of the insulin mitogenic pathway and insulin residence time on the receptor. A few studies on oral cancer and diabetes have shown an association between them while a few studies have indicated the opposite [13].

In our study, the mean Haemoglobin A1c (HbA1c) and mean blood glucose (MBG) of two groups showed similar findings between the two groups though it was lower 3.5%(

DOI: 10.46376/IJMR/2.3.2021.

p=0.070) and 9.6%(p=0.071) respectively in Group II (tobacco users with potentially malignant oral disorders)as compared to Group I(tobacco users without potentially malignant oral disorders).

These findings were similar to a study by **Mohsin *et al* in 2014** [14] revealing no significant association between premalignant lesions and diabetic patients in their study. **Muralidara *et al* in 2013.** also did not find any association between precancerous lesions and serum glucose levels. [15]

However, there are studies, which support an increase in cancer risk and mortality in diabetic patients. In the study done by **Thomas et al in 2004,** analyzing the risk factors of leukoplakia, he found that diabetic patients are three times more associated with leukoplakia than non-diabetic patients. They attributed this increased incidence of leukoplakia in diabetics to the metabolic and immunologic changes in the oral mucosa.[16]

Dikshit *et al*. in 2006 also found higher incidence of leukoplakia and lichen planus in diabetic patients in comparison with non-diabetic patients.[17]

A study was done by **Ujpál *et al*. in 2004** reveals 25.6% of Type I and 31.3% of Type II diabetic patients had glossitis and chronic cheilitis that are considered to be precursors of malignant transformations. 10.9% of Type I and 16.9% of Type II had benign tumors. 3.2% of Type I and 11% of Type II had leukoplakia or erythroplakia. There was higher incidence of gingival cancer (29%) and lip cancer (24%) in diabetics as compared to the non-diabetic group [18].

According to **Weinberg,** research and clinical observations during the past six decades have shown that: 1. Iron promotes cancer cell growth; 2. Hosts attempt to withhold or withdraw iron from cancer cells; and 3. Iron is a factor in prevention and in therapy of neoplastic disease. Thus deficient or excess intake of iron could have contributed to the carcinogenesis, habits could have altered iron intake as well as its metabolism and influenced tumorigenesis, and presence of the malignancy itself could have altered iron homeostasis [19].

However, in the present study, the mean Hemoglobin (Hb) was only slightly lowered 2.5% (p=0.054) in Group II (tobacco users with potentially malignant oral disorders) as compared to Group I (tobacco users without potentially malignant oral disorders), showing no

DOI: 10.46376/IJMR/2.3.2021.

significance of the role of iron in precancer and cancer carcinogenesis.

Various mechanisms for the induction of malignancy and premalignancy due to iron deficiency has been propounded. According to **Rajendran et al.,** submucous fibrosis appears to be an altered oral mucosa following prolonged period of chronic deficiency of iron and/or vitamin "B" complex especially folic acid, with hypersensitivity caused by local irritants and the resultant persistent juxta epithelial inflammatory response act as the initiating factor leading to a defective inflammatory-reparative response, culminating in fibrotic healing. A case control study on patients with precancerous diseases showed that serum iron was significantly depressed in such patients [20]

Jayadeep et al in 1997 reported that oral cancer patients have significantly lesser serum iron in oral cancer patients compared to those with normal controls and those with oral leukoplakias.[21]

Anuradha et al in 1993 observed that in patients with submucous fibrosis (all of whom were heavy tobacco and arecanut users too) serum iron decreased whereas the total tissue collagen content increased significantly in patients with advanced disease. They attributed the decrease in iron to utilization for collagen synthesis [22]

According to **Maguire (1982)**, whereas other forms of iron found physiologically might cause considerable oxidative damage naturally occurring protein-bound iron, such as ferritin and transferrin, which constitute major forms of transport and storage of iron in vivo, produce considerable mitigation of such toxicity in vivo. Iron deficiency reduces this protection and hence makes the tissue prone for genotoxic damage [23]

Lapenna et al (1995) suggest, from studies on smoking and ferritin, that cigarette-smoke mediated iron mobilization from ferritin may represent a specific prooxidant mechanism related to cigarette smoking in vivo. [24]

The limitations of our study include a relatively small sample size which could affect the outcomes of the study. Although the study groups were matched for age, gender, type and duration of habit, because the fact that PMODs and oral cancer are disorders of accumulative genotoxic damage development of such disorders at a later stage in an individual who currently is free from disease cannot be ruled out. Hence a longitudinal study

DOI: 10.46376/IJMR/2.3.2021.

would be ideal for studying the effect of these parameters on PMODs and oral cancer. Another drawback includes the heterogeneity of PMODs included in our study group. Disorders like leukoplakia and OSMF have different pathogenic pathways and hence may be associated with different systemic factors. Hence a stricter categorization of these lesions would give a clearer picture of the association of these metabolic parameters with different PMODs.

To conclude, the results of the present study indicate that a decreased serum lipid profile could be associated with higher risk of development of PMODs in tobacco abusers which in turn may predispose this group for development of oral cancer thus suggesting some role of lipid metabolism pathway in oral cancer. Although not statistically significant but a decrease in hemoglobin levels were also found to be associated with development of PMODs in this study. On the other hand the results of this study failed to demonstrate any relationship between serum glycemic status and development of PMODs. Prospective studies on a large sample of tobacco abusers followed up for a long duration will help in proving or disproving the role of metabolic derangement in oral carcinogenesis.

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