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Original Research Article

A HOSPITAL BASED PROSPECTIVE STUDY TO ASSESSED THE CORRELATION BETWEEN GLYCEMIC CONTROL, LIPID PROFILE AND ORAL LEUKOPLAKIA IN DIABETES PATIENTS

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Abstract

Background: Diabetes mellitus is rapidly becoming a common metabolic problem in urban and rural populations. The relationship between HbA1c and leukoplakia may be important with respect to diabetes. Even though there is a strong association between diabetes and leukoplakia, a causal mechanism for that has not been elucidated. The aim of this study to assessed the correlation between glycemic control, lipid profile and oral leukoplakia in diabetes patients. **Materials and Methods:** This is a case control study done on 207 cases of diabetes mellitus attending OPD/ IPD and Diabetic Care and Research Center, Department of Medicine, S.P. Medical College, Bikaner were taken as per WHO criteria. 190 cases without diabetes mellitus matched for confounding factors were taken as controls. Diagnostic criteria for abnormalities of the oral mucosa were in accordance with World Health Organization (WHO) guidelines. Confirmation of the diagnosis was done on histopathological examination by incisional biopsy. **Results:** Our study showed that mean age in study group was 53.64□17.07 years while in control group it was 43.07□18.25 years, and this difference was found statistically highly significant ($p<0.001$). On applying student 't' test the difference was found statistically highly significant ($p<0.001$) in education status in both groups. Out of total 207 study group 100 cases had their HbA1c level >9.0 while in control group no case had HbA1c >9.0. Mean HbA1c in study group was 8.93□1.54% while in control group it was 5.08□0.6%, and this difference was found statistically highly significant ($p<0.001$). Leukoplakia was present in 9(4.4%) cases of study group and 3(1.6%) cases of control group. The present study showed multiple linear regression analysis of different parameters in relation to leukoplakia in study and control groups. Increasing trend was shows at all the time when we add BMI, WHR, TG, TC, HDL, LDL, RBS and HbA1c. **Conclusion:** We concluded that occurrence of leukoplakia was higher in diabetics patients compared to normoglycemic healthy individuals. These findings necessitated regular clinical examinations to ensure early diagnosis and prompt management of leukoplakia in diabetes and dyslipidemic patients.

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 415 million in 2015. Based on current trends, the International Diabetes Federation projects that 642 million individuals will have diabetes by the year 2040.[1]

Diabetes can affect many different organ systems in the body and, over time, can lead to serious complications. Complications from diabetes can be classified as microvascular or macrovascular. Microvascular complications include nervous system damage (neuropathy), renal system damage (nephropathy) and eye damage (retinopathy).[9]

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Similarly, a number of oral health complications are frequently associated with DM.[10] These include various inflammatory diseases, reduced saliva secretion, and oral mucosal pathologies. Further, inflammatory diseases such as gingivitis, periodontitis, candidiasis, stomatitis, benign migratory glossitis or geographic tongue (GT), median rhomboid glossitis, and angular cheilitis have been reported frequently in various studies.1-3 DM predisposes an individual to bacterial and fungal infections as well, including those caused by Candida species.[4]

A previous study 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 were more incidences of gingival cancer (29%) and lip cancer (24%) as compared to the non-diabetic group.[9]

In 1978 a World Health Organization (WHO) group defined oral leukoplakia as: "A white patch or plaque that cannot be characterized clinically or pathologically as any other disease".[11] It is therefore a diagnosis of exclusion from other oral white lesions such as leukokeratosis, infective lesions (candidiasis, syphilitic oral lesion, oral hairy leukoplakia caused by Epstein Barr virus), lichen planus, lupus erythematosus, dyskeratosis congenita, white sponge nevus, submucosal fibrosis and frank carcinomas.11-13 It is common in adults beyond 40 years of age, and affects 1% of the total population.[14]

Chewing, smoking and consumption of alcoholic beverages have become common social habits in India. The prevalence of these habits was found to be more among men as compared to women. The prevalence was higher among the rural population and those with no formal education.[15]

Betel quid chewing with or without tobacco, smoking and alcohol drinking are well-established risk factors for pre-malignant oral diseases.[16] Recently attempts have also been made to investigate an association between clinical variables and risk of premalignant oral diseases. Past history of diabetes has been linked with development of pre-malignant oral diseases in a few studies.[17,18] An association between diabetes mellitus and periodontal and oral diseases, and various inflammatory lesions in oral cavity has also been demonstrated.

Smoking, drinking, and chewing have been positively associated with oral lesions such as oral submucous fibrosis (OSF), leukoplakia, and oral lichen planus, which has the potential for malignant transformation.[11] Higher occurrence of leukoplakia and cancer are observed in OSF patients and it is believed to be an important risk factor for oral cancer among youth.[19]

The estimated annual rate of oral leukoplakia malignant transformation is 1.36% (0.69-2.03%). Smoking and drinking alcohol are main risk factors for this disease,[20] diabetes is an emerging risk factor related to different pathological states in the oral cavity including premalignant and malignant lesions.[21]

It has been suggested that poor diabetic control is associated with an increased cancer risk due to enhanced oxidative damage to DNA.[22] Production of reactive oxygen species and lipid peroxidation are increased in diabetic patients, especially in those with poor diabetic control and hyper-triglyceridemia. Increased oxidative damage can be due to superoxide radical generation by monocytes through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. These superoxides can undergo either enzymatic or nonenzymatic dismutation to generate hydrogen peroxide. In the presence of transition metals, such as Fe++ and Cu++, both these substances contribute to the generation of highly reactive hydroxyl radicals causing damage to cells.[22] Those with uncontrolled diabetes are at even greater risk of developing oral cancer. In diabetic patients, T-cell function as well as the cellular immune response is impaired thus, diminished immunity may facilitate the action of carcinogens. In addition, there can be microangiopathy,[23] in the gingival tissues causing tissue hypoxia and a reduced blood supply, which together with the impaired cellular immune response may play a role in the development of oral cancer.

The relationship between HbA1c and leukoplakia may be important with respect to diabetes. Even though there is a strong association between diabetes and leukoplakia, a causal mechanism for that has not been elucidated. The aim of this study to assessed the correlation between glycemic control, lipid profile and oral leukoplakia in diabetes patients.

MATERIALS AND METHODS

This is a case control study done on 207 cases of diabetes mellitus attending OPD/ IPD and Diabetic Care and Research Center, Department of Medicine, S.P. Medical College, Bikaner were taken as per WHO criteria. 190 cases without diabetes mellitus matched for confounding factors were taken as controls. Controls were hospital staff or attendants unrelated to cases. Exclusion and inclusion criteria were applied to both case and control.

Inclusion Criteria

1. Written consent given for participation by case and control.
2. All male and female patients of type 1 and type 2 diabetes mellitus
3. Age group: >18 years.

Diagnostic criteria for diabetes mellitus.[24]

1. Fasting blood sugar > 7.0mmol/L(126mg/dl) or
2. HbA1C > 6.5%
3. Two-hour plasma glucose > 11.1mmol/L(200mg/dL) during an oral glucose tolerance test
4. Symptoms of diabetes plus random blood glucose concentration > 11.1mmol/L(200mg/dL).

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Classification and Staging System of Oral Leukoplakia.[25]

Size of Leukoplakia (L)

L1- size of single or multiple leukoplakias together <2cm

L2- size of single or multiple leukoplakias together 2-4 cm

L3- size of single or multiple leukoplakias together >4cm

Lx-size not specified.

Pathology (P)

P0- no epithelial dysplasia (includes" no or perhaps mild epithelial dysplasia

P1-mild or moderate epithelial dysplasia

P2-severe epithelial dysplasia

Px-absence or presence of epithelial dysplasia not specified in the pathology report.

Oral Leukoplakia Staging System

Stage 1- L1P0

Stage 2-L2P0

Stage 3-L3P0 or L1L2P1

Stage 4-L3P1 or any LP2

Criteria of dyslipidimia (NCEP ATP 3 GUIDELINES): (National Cholesterol Education Program, Adult Treatment Panel 3).

LDL Cholesterol

<100	Optimal
100-129	Near optimal/ above optimal
130-159	Borderline high
160-189	High
>190	Very high

Total Cholesterol

<200	Desirable
200-239	Borderline high
>240	High

HDL Cholesterol

< 40	Low
>60	High

Triglycerides

<150	Normal
150-199	Borderline high
200-499	High
>500	Very high

VLDL

<30	Optimal
>30	High

Exclusion Criteria

1. Not giving written consent.
2. Age < 18 year
3. Patients suffering from other co-morbidities like, chronic liver disease, chronic kidney disease, oral malignancy, chemotherapy, hypothyroidism, hyperthyroidism etc.
4. Patients suffering from infections like bacterial, fungal, viral (HIV, HBV & HCV) etc.
5. Patients with ill-fitting dentures, gingivitis, peridontitis, candidiasis, stomatitis, angular cheilitis, lichen planus and oral submucosal fibrosis.

Methods

The study was approved by the institutional review board and informed consent was obtained by all patients prior to study entry. Patient's demographic, anthropometric, clinical characteristics were recorded and filled in the proforma.

During hospitalization, the patients were evaluated in terms of the detailed history and clinical examination to evaluate oral mucosal lesions. Blood samples were taken from a peripheral vein at the time of first consultation. Hematology and biochemistry were determined by routine techniques using an automated analyser.

Procedure

Serum lipid value were estimated by mixing 10µl serum sample with 1000µl of working reagent individual lipids respectively and this mixture was incubated at 37°C for 5 minutes. Random blood sugar was determined by glucometer based on gluco-oxidase method (SUGARCHECK). Glycemic control was assessed by HbA1c. HbA1C was determined by ion exchange chromatography.

Clinical consultations for oral lesions were taken from Dentist. Oral examination by dentist visual examination of the mouth was carried out by a single examiner who was supervised and assessed by an oral medicine specialist. Extraoral and intraoral examination was performed under electrical overhead lights using a mouth mirror, tweezers, gauze, and a wooden tongue depressor. Diagnostic criteria for abnormalities of the oral mucosa were in accordance with World Health Organization (WHO) guidelines.26 Confirmation of the diagnosis was done on histopathological examination by incisional biopsy.

Statistical Analysis

Data thus collected were analysed and chi square test, student 't' test, ANOVA test, regression analysis, multiple linear regression analysis were used by using SPSS 17.0, considering p value <0.05 as statically significant.

RESULTS

Our study showed that mean age in study group was 53.64□17.07 years while in control group it was 43.07□18.25 years, and this difference was found statistically highly significant (p<0.001). Most of patients were males in both study and control group (64.7% and 67.4% respectively).

Our study showed that majority of cases belonged to rural area in both study and control groups (58% and 66.8% respectively) while 42% cases in study group belonged to urban area and in control group 33.2% cases belonged to urban area. On applying student 't' test the difference was found statistically highly significant (p<0.001) in education status in both groups (table 1).

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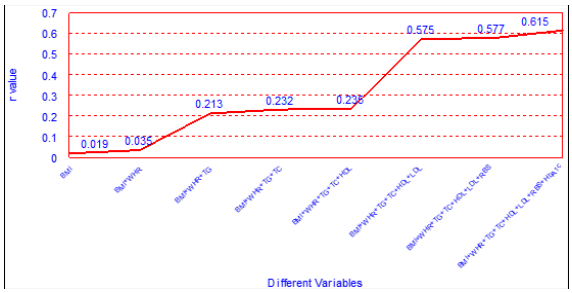
According to personal history, 49(23.7%) and 37(19.5%) cases of study and control group were smokers respectively, while 15(7.2%) and 15(7.9%) of study and control group taking alcohol respectively, and tobacco chewers in study and control groups were 27(13%) and 54(13.6%) cases respectively (table 2).

Out of total 207 study group 100 cases had their HbA1c level >9.0 while in control group no case had HbA1c >9.0. Mean HbA1c in study group was 8.93□1.54% while in control group it was 5.08□0.6%, and this difference was found statistically highly significant (p<0.001) (table 3).

Leukoplakia was present in 9(4.4%) cases of study group and 3(1.6%) cases of control group (table 4). Graph 1 shows multiple linear regression analysis of different parameters in relation to leukoplakia in study and control groups. Increasing trend was shows at all the time when we add BMI, WHR, TG, TC, HDL, LDL, RBS and HbA1c.



Graph 1: Multiple linear regression analysis of different parameters in relation to leukoplakia in study and control groups

Table 1: Distribution of cases according to Demographic profile in both groups

Demographic profile		Study group	Control group	P- value
Age (yrs)		53.64±17.07	43.07±18.25	<0.001*
Gender	Male	134 (64.7%)	128 (67.4%)	0.580
	Female	73 (35.3%)	62 (32.6%)	
Residential area	Rural	120 (58%)	127 (66.8%)	0.069
	Urban	87 (42%)	63 (33.2%)	
Education	Illiterate	134 (64.7%)	80 (42.1%)	<0.001*
	Primary	14 (6.8%)	29 (15.3%)	
	Middle	17 (8.2%)	22 (11.6%)	
	Secondary	21 (10.1%)	29 (15.3%)	
	Sr. Secondary	3 (1.45)	2 (1.1%)	
	Graduate	1 (0.5%)	18 (9.5%)	
	Post Graduate	17 (8.2%)	10 (5.3%)	

Table 2: Distribution of case according to personal history in both groups

Personal History		Study Group		Control Group		Total		χ^2	p
		No.	%	No.	%	No.	%		
Smoking	No	158	76.3	153	80.5	311	78.3	1.029	0.310
	Yes	49	23.7	37	19.5	86	21.7		
Alcohol	No	192	92.8	175	92.1	367	92.4	0.06	0.807
	Yes	15	7.2	15	7.9	30	7.6		
Tobacco Chewing	No	180	87.0	163	85.8	343	86.4	0.115	0.735
	Yes	27	13.0	27	14.2	54	13.6		

Table 3: Distribution of cases according to HbA1c in both groups

HbA1c	Study Group		Control Group		Total	
	No.	%	No.	%	No.	%
4.5-5.6	0	-	147	77.4	147	37.0
5.7-6.4	1	0.5	43	22.6	44	11.1
6.5-7.0	17	8.2	0	-	17	4.3
7.1-8.0	50	24.2	0	-	50	12.6
8.1-9.0	39	18.8	0	-	39	9.8
>9.0	100	48.3	0	-	100	25.2
Total	207		190		397	
Mean	8.93		5.08			
SD	1.54		0.66			
t	31.935					
p	<0.001					

Table 4: Distribution of cases according to finding of leukoplakia in both groups

Leukoplakia	Study Group		Control Group		Total	
	No.	%	No.	%	No.	%
Positive	9	4.4	3	1.6	12	3.1
Normal	198	95.7	187	98.4	383	96.5
Total	207		190		397	
χ^2	2.702					
p	0.259					

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DISCUSSION

Leukoplakia is the most common potentially malignant disorder of the oral mucosa, recently redefined as "a white plaque of questionable risk having excluded other known disorders that carry no increased risk factor for cancer". Tobacco in different forms has been described as the most common incriminating factor for such lesions.[27-29] However, other factors, depending on the socio-cultural habits of the patients that lead to chronic irritation of oral and buccal mucosa may also be contributory. It starts as a thin homogeneous greyish white plaque either well defined or blending with the surrounding tissue. The lesion enlarges to leathery appearance with surface fissures (thick homogeneous leukoplakia). Some lesions develop surface irregularities (granular or nodular leukoplakia), warty papillary surface projections (verrucous leukoplakia), or mixed red and white lesions (speckled leukoplakia or erythroplakia). In present study, majority of cases in study group belonged to age group >60 years (39.6%) followed by 41-60 years (36.2%), 21-40 years (18.4%) while least cases belonged to age group <20 years (5.8%). Mean age in study group was 53.64±17.07 years while in control group it was 43.07±18.25 years. Similar results were observations by Al-Maweri et al,[30] where they found mean age of study group patients was 54.71±8.48 years and in control group it was 53.04±12.06 years. Miesel et al,[31] in their study observed that mean age in study group was 55.2±15.5 years while in control group mean age was 55.2±15.6 years, supportive to our results.

Out of total 207 study group patients, 134 were male and 73 were female with a male to female ratio 1.84:1, suggestive of male predominance. Mishra et al,[32] in their study observed that 1570 (53.76%) were male and 1350 (46.24%) female with male to female ratio 1.16:1. Thomas et al,[33] also found a male to female predominance in their study with male to female ratio was 1.71:1 similar to our results. Males were at a higher risk of developing OSF and leukoplakia; however, the risk of cancer was not significantly different between the two genders. This difference could be related to the difference in habit frequency between male and female individuals, diet, or other physiological factors. Alcohol drinking and smoking not socially accepted in India, specially for women.

In present study, majority of cases belonged to rural area in both study and control groups (58% and 66.8% respectively) while 42% cases in study group belonged to urban area and in control group 33.2% cases belonged to urban area. In a study conducted by Saghravanian et al,[34] found that among the malignant lesions that were studied in their study, most of them were located peripherally and 6 cases were located centrally. In a study with smaller sample size, Delavarian et al,[35] reported 41 peripheral and 3 central cases of oral cancer, respectively.

In present study, in study and control group majority of cases were illiterate (64.7%; 42.1% respectively) while least common educational status was post graduate. Thomas et al,[33] found that the level of education was higher among the controls than the cases; the highest percentage of cases were in the illiterate category which supports our results. This difference could be related to poor oral hygiene and unawareness about risk of disease.

Gupta et al,[36] in their study described that among other factors which could modify the risk of oral lesions, alcohol appeared to increase the risk of OSF, leukoplakia, and lichen planus but not oral cancer. It is difficult to explain why alcohol should increase the risk of oral precancerous lesions but not oral cancer. Smoking duration was only marginally related with oral cancer at 95% level of confidence, increasing by 0.007 with every extra month of smoking. A relatively lesser impact of smoking may be due to the indirect and relatively shorter duration of contact with tobacco in the oral cavity in comparison to the habit of tobacco chewing. Alcohol duration related negatively with oral cancer and leukoplakia, decreasing by 0.01 for oral cancer and leukoplakia with every extra month of the alcohol habit; however, the mechanism of the same remains beyond understanding. It is possible that smoking and alcohol are greater risk factors in the presence of other habits such as chewing tobacco/pan masala but do not seriously affect the risk of oral lesions by themselves.

In present study out of total 207 study group 100 cases had their HbA1c level >9.0 while in control group no case had HbA1c >9.0. Mean HbA1c in study group was 8.93±1.54% while in control group it was 5.08±0.6% and this difference was found statistically highly significant ($p<0.001$). In study group, we found that patients having poor glycemic control had increased risk of leukoplakia as compared to control group.

Meisel et al,[31] in their study observed that HbA1c was significantly associated with leukoplakia, indicating an increase in the probability of the outcome: HbA1c OR 1.51, thereby exhibiting significant interaction with current smoking (HbA1c x smoking, P=0.012). In non-smokers, the leukoplakia probability was low at normoglycemic state. But there was a more pronounced increase in the probability of having leukoplakia with the increasing metabolic factor HbA1c as compared with smokers. Smokers were at increased risk even when having low HbA1c levels.

An association has been reported between diabetes mellitus and premalignant oral lesions among Keralite women in India.[37] Another study also reported a significantly higher prevalence of potentially malignant disorder including leukoplakia among type 2 diabetes mellitus patients when compared to non-diabetics.[38]

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Mohsin et al in their study found that the prevalence of leukoplakia was 3.5% in diabetic individuals with no significant difference as compared with the controls. The high prevalence of leukoplakia in above mentioned study could be attributed to a high number of smokers among the diabetics. Type 2 DM patients who smoke are more prone to leukoplakia as compared to those who do not smoke.[9] The present study had less number of smokers compared with the other similar studies.[38]

Albrecht et al,[39] in their study found that the prevalence of oral leukoplakia in diabetic patients was 6.2%, as compared to 2.2% in the healthy controls, The prevalence of leukoplakia was directly related to the duration of the diabetic metabolic disorder, as leukoplakia developed mainly in the second year of established diabetes. Considering the type of treatment, the highest prevalence was found among insulin-treated diabetics and diabetic smokers were more often affected (11.2%). than non-smokers. It is also possible that a positive association between diabetes mellitus and premalignant lesions might occur due to shared risk factors. Both are associated with late onset, as well as a diet high in fat and energy and low in fibre. Increased consumption of saturated fats increases the risk of diabetes mellitus, but recently it has been suggested that it also increases the risk of oral cancer.40 More elaborate studies are required to show a significant association between diabetes mellitus and oral cancer, as these initial findings may be coincidental.

In present study, when we applied multiple linear regression analysis in different parameters like BMI, WHR, TG, TC, HDL, LDL, RBS and HbA1c, r value was increased all the time when we add one parameter to another. We found that with increasing r value, the risk of leukoplakia was also increased.

Meisel et al,[31] suggest that results from the logistic regression that there is a continuously increasing risk with increasing levels of glycosylated hemoglobin or of LDL-c. Accordingly, the risk seems to be related to quantitative metabolic disturbances rather than to distinct cases of diabetes. As in other tissues, the diabetic metabolism leads to profound deterioration in the oral cavity which may predispose for oral leukoplakia.[41] The association of leukoplakia with increasing LDL-c/HDL-c ratios could be explained by the disturbed lipid metabolism frequently seen in diabetic patients.[42]

CONCLUSION

We concluded that occurrence of leukoplakia was higher in diabetics patients compared to normoglycemic healthy individuals. Higher occurrence in diabetics was positively correlated with poor glycemic control. The risk was further increased in association with dyslipidemia. Smoking, tobacco chewing and alcoholism significantly increased the risk in poorly controlled diabetes with dyslipidemia. These findings necessitated regular clinical examinations to ensure early diagnosis and prompt management of leukoplakia in diabetes and dyslipidemic patients.

Limitation

As the sample size was small, the correlation may not be truly reflective of etiopathogenesis of the disease in the population. Large scale studies are required for further correlation between glycemic control, lipid profile and oral leukoplakia in diabetes.

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