ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Assessment of Salivary Function and Prevalence of Candidal and Noncandidal Oral Soft Tissue Pathologies in Type 1 Diabetics: A Cross Sectional Study.

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ABSTRACT

`Diabetes mellitus is a common disease with concomitant oral manifestations that impact dental care. The prevalence of oral soft tissue pathologies in type 1 diabetics has been reported scarcely in literature. This paper reports the prevalence of candidal and noncandidal oral soft tissue pathologies in type 1 diabetics and the assessment of salivary function in them. Stimulated and unstimulated salivary flow rates were recorded to assess salivary function in type 1 diabetics. The candidal and noncandidal oral soft tissue pathologies were assessed by clinical examination and by analysis of laboratory data. The stimulated salivary flow rate was reduced when compared to the control individuals while there was no significant difference in their unstimulated salivary flow rates. Fissured tongue was more prevalent in the diabetic population. No candidal lesions were seen. Coexistence of type 1 diabetes and candidiasis is not always present but is also influenced by other factors like glycemic control

Keywords: Salivary flow rate, soft tissue pathology, Type 1 diabetes, glycemic control.

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ISSN: 0975-8585

INTRODUCTION

Diabetes mellitus is defined as a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin.[1] According to the updated WHO classification of diabetes, there are two major forms of the disease: Type 1 and Type 2 (formerly, respectively, insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM)). [2] Approximately 10–20% of all diabetic patients having juvenile onset insulin-dependent disease are classified as Type 1. Type 1 diabetes is one of the most frequent chronic diseases in children. These patients usually have rapid onset of symptoms and are characterized by a virtually complete inability to produce insulin. Type 2 diabetes is non-insulin dependent. It is the most common type of diabetes often associated with obesity and is characterized by slow onset of symptoms, usually after 40 years of age. Other less prevalent forms of diabetes include gestational diabetes seen during pregnancy and diabetes secondary to other medical conditions. [3]

Reported oral health complications associated with diabetes that may be encountered by dental practitioners include xerostomia, gingivitis, periodontitis, odontogenic abscesses, tooth loss, altered wound healing, sialadenitis, sialadenosis and soft tissue lesions of the tongue and mucosa. [1, 3] The frequent occurrence of Candida infections in patients with diabetes mellitus has been recognized for many years. [4]

Although many studies have evaluated oral diseases in patients with diabetes mellitus there have been conflicting findings regarding the prevalence of some conditions. This may be a reflection of the different pathophysiologic behaviours of the 2 clinical types of diabetes: type 1 or insulin dependent diabetes mellitus and type 2 or noninsulin dependent diabetes mellitus. Other factors that may be responsible for the different findings include variations in glycemic control, duration of disease, or age of the patients. Furthermore, a number of studies may be methodologically flawed by not having compared disease prevalence in subjects with diabetes with that in control subjects without diabetes. [5]

Hence the present study was conducted to assess salivary flow rate, candidal carrier state, candidal lesions and noncandidal oral soft tissue pathologies in patients with type 1 diabetes and to assess possible associations between oral soft tissue pathologies with age, gender, medication use, salivary function, denture use, smoking habits, glycemic control and diabetic complications of nephropathy, neuropathy, retinopathy and peripheral vascular disease.

MATERIALS AND METHODS

Our study enrolled 200 subjects, 100 with Type1 diabetes visiting “Bangalore Diabetes Hospital” and 100 age and sex matched nondiabetic control subjects visiting outpatient Department of Oral Medicine and Radiology, Rajarajeswari Dental College and Hospital, Bangalore, India. Type 1 diabetics ≥ 7 years and < 20 years with an onset age less than 17 years were included in the study. Patients who were critically ill requiring intensive care and uncooperative patients were excluded from the study.

Before the oral health examination an informed consent was obtained from the patients participating in the study. Each subject was interviewed, and the questionnaire was reviewed for completeness. Demographic data included age, weight, height, race, gender, income, education, and marital status. The medical history included information concerning allergies, heart murmurs, pregnancy, current medications, hospitalizations, prosthetic joint replacement, status of current medical care, and significant previous illnesses. Tobacco use, including lifetime use, start age, consumption, and current use were assessed. Alcohol consumption data, including daily consumption levels of beer, wine, and liquor, were determined from the questionnaire. A self-report of current prescription and over-the counter medication use was recorded. The dental history section of the questionnaire solicited information regarding previous dental care, most recent dental visits, oral hygiene habits, fluoridation, perceived treatment needs, dental anxiety, and dental insurance.

For clinical examination electrical dental chair with illumination, kidney tray, mouth mirror, probe, gauze, surgical gloves and mouth mask were used. For collection of saliva and cytologic smears graduated test tubes, funnel, tongue blade or blunt spatula, glass cutter, metallic scale, slides, compound microscope were used. Prior to clinical examination the glycosylated hemoglobin values of the type 1 diabetics was determined.

The first component of the study included timed stimulated and unstimulated whole saliva collection. Since it is best to collect saliva in the morning an early morning saliva sample was collected from the patients between 7:30 am and 8:00 am. The subjects were made to sit comfortably in a chair and were asked to refrain from eating, drinking or smoking for 90 minutes prior to the collection. The unstimulated salivary flow rate was determined by instructing patients not to swallow for 5 minutes and then having to expectorate into a funnel inserted into a graduated collection vial. The stimulated salivary flow rate was determined by swabbing the laterodorsal surface of the tongue with lemon juice every 30 seconds for a period of 2minutes and then saliva was expectorated into the graduated vial. The readings were recorded in ml/min.

The second component of the study included complete intraoral soft tissue examination which was performed with the help of a dental mirror and gauze square. The diagnosis of any oral soft tissue pathosis was established based on onset, duration, oral habits, clinical appearance, history of trauma, and previous episodes. Abnormalities were recorded on a checklist of common oral lesions. The location and description of the lesions was also recorded.

The third component of the study included making cytosmears from posterior middle dorsal surface of tongue using a tongue blade or a blunt spatula. A glass slide was marked with the help of a glass cutter into an area of $2cm^2$. The material was spread on the glass slide on the marked area of approximately 2 cm^2.The slide was immediately fixed with a spray fixative and was allowed to air dry. Slides were stained with Periodic Acid Schiff stain and the number of pseudohyphae in the densest $1cm^2$ area were counted. Values for Candida counts were summarized for statistical analysis as absent, any present and greater than $10/cm^2$.

Descriptive statistical analysis was carried out in the present study. Results on continuous measurements were presented on Mean $\pm$ SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance. 2x5 Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

The study comprised of total 200 cases that were divided into two groups. Group I comprised of 100 type 1 diabetic cases out of which 53 were males and 47 were females, age range varied from 7-20 years, mean and standard deviation of 12.73±3.06. Group II comprised of 100 nondiabetic subjects who were age and sex matched with the subjects. The male: female ratio in our patients was 1.1. 97% of the patients came from a urban locality while 2% were from a rural background.

78% of the patients with type 1 diabetes had an onset age of the disease ranging between 6-10 years, while 22% of the patients had an onset age between 1-5 years. In Type 1 diabetics the glycosylated haemoglobin levels were less than 5g/dl in 17 patients, between 5-8g/dl in 60 patients, between 8-10g/dl in 11 patients and >10g/dl in 12 patients with a mean value of 7.02±2.26g/dl .

The unstimulated salivary flow rate in type 1 diabetics ranged from 0.31±0.14ml/min when compared to 0.32±0.09ml/min in the controls with a P value of 0.193. The stimulated salivary flow rate in type 1 diabetics ranged from 2.79±1.17ml/min when compared to 3.83±0.69ml/min in the controls with a P value of <0.001** (Table 1). Only one patient presented with retinopathy. No other diabetic complications were present in any of the diabetic subjects.

Table 1: Comparison of Unstimulated and Stimulated Salivary flow rate in Study and Controls

Salivary flow ml/min	Controls	Study Group	P value
Unstimulated	0.32±0.09	0.31±0.14	0.493
Stimulated	3.83±0.69	2.79±1.17	<0.001**

Type 1 diabetics manifested more oral soft tissue pathologies (46.0%) compared to controls (40.0%) with a P value of 0.391. The oral soft tissue pathologies were more prevalent among males in both the study

groups (Table 2). There was no evidence of clinical manifestation of candidiasis in either the Type 1 diabetics or control subjects. Candida pseudohyphae were absent in the smears obtained from both the subjects and control population studied.

Table 2: Comparison of Soft tissue pathology in two groups studied

Soft tissue pathology	Controls (n=100)	Study group (n=100)	P value
Absent	60(60.0%)	54(54.0%)	0.391
Present	40 (40.0%)	46(46.0%)	
• Male	21 (21.0%)	25(25.0%)	0.502
• Female	19(19.0%)	21(21.0%)	0.724

The noncandidal oral soft tissue pathologies seen commonly in type 1 diabetics were fissured tongue (17%, P= 0.054), marginal gingivitis (14% P= 0.259), migratory glossitis (4%, P=0.683), irritation fibroma (4%, P= 0.369), aphthous ulcer (3%, P = 1.0), traumatic ulcer (3%, P = 0.621), angular cheilitis (1%, P = 0.621). The noncandidal oral soft tissue pathologies seen commonly in the control subjects were marginal gingivitis (20%, P = 0.259), fissured tongue (8%, P= 0.054), aphthous ulcer (4%, P = 1.0), angular cheilitis (3%, P== 0.621), herpes labialis (3%, P= 0.246), migratory glossitis (2%, P=0.683), atrophy of tongue papillae (2%, P = 0.497), traumatic ulcer (1%, P= 0.621) and irritation fibroma (1%, P= 0.369) (Table 3).

Table 3: Comparison of Soft tissue pathology in two groups studied

Soft tissue pathology	Controls (n=100)	Study group (n=100)	P value
1.Angular cheilitis	3(3.0%)	1(1.0%)	0.621
2.Aphthous ulcer	4(4.0%)	3(3.0%)	1.000
3.Atrophhy of tongue papillae	2(2.0%)	0	0.497
4.Fissured tongue	8(8.0%)	17(17.0%)	0.054+
5.Gingivitis	20(20.0%)	14(14.0%)	0.259
6.Herpes labialis	3(3.0%)	0	0.246
7.Irritation fibroma	1(1.0%)	4(4.0%)	0.369
8.Migratory glossitis	2(2.0%)	4(4.0%)	0.683
9.Traumatic ulcer	1(1.0%)	3(3.0%)	0.621
10.Lichen planus	0	0	NS
11.Median rhomboid glossitis	0	0	NS
12.parotid enlargement	0	0	NS
13.Candidiasis	0	0	NS
14.Candidal count per sq cm	0	0	NS

Table 4: Comparison of Soft tissue pathology between male and female in Study Group

Soft tissue pathology	Male (n=53)	Female (n=47)	P value
1.angular cheilitis	1 (1.9%)	0 (0%)	1.000
2.aphthous ulcer	3 (5.7%)	0 (0%)	0.245
3.Atrophy of tongue papillae	0 (0%)	0 (0%)	-
4.Fissured tongue	7 (13.2%)	10 (21.3%)	0.284
5.Gingivitis	8 (15.1%)	6 (12.8%)	0.738
6.Herpes labialis	0 (0%)	0 (0%)	-
7.Irritation fibroma	3 (5.7%)	1 (2.1%)	0.620
8.Migratory glossitis	2 (3.8%)	2 (4.3%)	1.000
9.Traumatic ulcer	1 (1.9%)	2 (4.3%)	.599
10.Lichen planus	0 (0%)	0 (0%)	-
11.Median rhomboid glossitis	0 (0%)	0 (0%)	-
12.parotid enlargement	0 (0%)	0 (0%)	-
13.Candidiasis	0 (0%)	0 (0%)	-
14.Candidal count per sq cm	0 (0%)	0 (0%)	-

Only fissured tongue was found to be more prevalent among the diabetic population with a P value of 0.054+. Other oral soft tissue pathologies like lichen planus, median rhomboid glossitis, parotid enlargement were absent in both diabetic and control population.

Lesions found more commonly in males in the study group included marginal gingivitis (15.1%, P = 0.738), fissured tongue (13.2%, P =0.284), irritation fibroma (5.7%, P = 0.620) angular cheilitis (1.8%), aphthous ulcer (5.7%, P = 0.245), migratory glossitis (3.8%, P = 1.0), traumatic ulcer (1.9%, P = 1.0%) and angular cheilitis (1.9%, P = 1.0%). Lesions commonly found in females in the study group included fissured tongue (21.3%, P = 0.284), gingivitis(12.8%, P= 0.738), migratory glossitis (4.3%, P = 1.0), traumatic ulcer (4.3%, P = 0.599) and irritation fibroma (2.1%, P= 0.620) (Table 4).

Lesions found more commonly in males in the control group included marginal gingivitis (20.8%, P= 0.941),angular cheilitis (3.8%, P = 1.0), herpes labialis (3.8%, P = 1.0), atrophy of tongue papillae (3.8%, p = 0.497), traumatic ulcer (1.9%, P = 1.0), migratory glossitis (1.9%, P = 1.0),fissured tongue (1.9%, P = 0.339) and aphthous ulcer (1.9%, P = 0.339) . Lesions commonly found in the females in the control group included gingivitis (19.1%, P = 0.941), aphthous ulcer (6.4%, P = 0.339), fissured tongue (6.4%, P = 0.339), migratory glossitis (2.1%, P= 1.0), herpes labialis (2.1%, P= 1.0), angular cheilitis (2.1%, P= 1.0) and irritation fibroma (2.1%, P = 0.470) (Table 5).

Table 5: Comparison of Soft tissue pathology between male and female in Control group

Soft tissue pathology	Male (n=53)	Female (n=47)	P value
1.angular cheilitis	2 (3.8%)	1 (2.1%)	1.000
2.aphthous ulcer	1 (1.9%)	3 (6.4%)	0.339
3.Atrophhy of tongue papillae	2 (3.8%)	0 (0%)	0.497
4.Fissured tongue	1 (1.9%)	3 (6.4%)	0.339
5.Gingivitis	11 (20.8%)	9 (19.1%)	0.941
6.Herpes labialis	2 (3.8%)	1 (2.1%)	1.000
7.Irritation fibroma	0 (0%)	1 (2.1%)	0.470
8.Migratory glossitis	1 (1.9%)	1 (2.1%)	1.000
9.Traumatic ulcer	1 (1.9%)	0 (0%)	1.000
10.Lichen planus	0 (0%)	0 (0%)	-
11.Median rhomboid glossitis	0 (0%)	0 (0%)	-
12.parotid enlargement	0 (0%)	0 (0%)	-
13.Candidiasis	0 (0%)	0 (0%)	-
14.Candidal count per sq cm	0 (0%)	0 (0%)	-

DISCUSSION

Diabetes mellitus is a disease affecting the salivary gland functioning, and thus altering the salivary constituents and function. Conceivably this may be due to changes in the circulation to the salivary glands, autonomic dysfunction, dehydration and osmotic diuresis, destruction of the acinar parenchyma or other changes. [6] The exact cause for xerostomia is unknown but maybe related to polyuria or to alterations in the basement membranes. [7] Our study conducted to estimate the salivary flow rate in type 1 diabetics revealed no difference in unstimulated salivary flow rate. This observation is in accordance with studies by Jorda LM, Lima et al and Miralles L. However the stimulated salivary flow rate was significantly reduced among the diabetics when compared with controls.

Hence it could be inferred that xerostomia is a common complication of diabetes, the cause of which needs to be explored by more qualitative examination of saliva, such as increased concentrations of glucose in saliva, immune factors contained in saliva, or the influence of antidiabetic therapy.

It is generally acknowledged that patients with diabetes mellitus are more susceptible to fungal infections, particularly Candida albicans, than are patients without diabetes. [5] Although this has not been the finding of all workers. [4] Factors unrelated to diabetes may influence candidal carriage, these include gender, smoking, oral site, medications, use of dentures, and the quantity and quality of the saliva. [5]

Odds et al inferred from their study that the quantities of yeast recovered were significantly higher among diabetics who had an acute disturbance of diabetic control than in well controlled patients. [4]

Tapper Jones et al inferred that the frequency of candida isolation was significantly higher in dentate diabetics than controls but a significant rise in candidal density occurred only amongst denture wearers with diabetes. Smoking increased the candidal carrier rate both in diabetics and controls. No correlation was found between the age of diabetics or the duration of diabetes and the carrier rate. [9]

Guggenheimer et al and Peters et al in1966 proposed that no significant increase in Candida pseudohyphae were detected in diabetics when compared with controls. The disparity in results was attributed to the differences in sampling techniques, sites sampled and selection of subjects. [4]

Our study showed no Candidal carriage amongst both type 1 diabetics and controls which is in accordance with Guggenheimer et al and Peters et al. However the mean glycosylated Hb in our study group was 7.02±2.26 which is considered to be good glycemic control and could be one of the reasons for the negative candidal carrier state. All our samples were dentulous and none of our patients had prosthesis**.** Abstinence from smoking and denture use could therefore have contributed to the absence of candidal carrier state in our cohort of type 1 diabetics.

Aly et al proposed that by the swab technique yeasts were isolated more frequently from the tongue followed by the palate, floor of the mouth and the angles of the mouth. [10] If Candida albicans is present in the oral cavity , a swab of the oral tissues has much greater probability as a positive source of isolation of the yeast than a random sample of saliva. [10] Arendorf and Walker S (1980) in their study used similar culture and cytosmears in recording the prevalence of Candida. Culture findings recorded a higher prevalence than smears. [11] However Tapper Jones et al inferred that imprint cultures were more sensitive than the mouthwash technique for detecting carriers of C.albicans. [9]

Our study was performed by making tongue smears from the posterior dorsal surface for assessment of Candida. The negative Candidal isolation obtained in our study may indicate that smears are less sensitive for detecting carrier state.

These findings suggest that the subjects with IDDM are not likely to carry Candida pseudohyphae, but are susceptible to candidal infections, particularly when host resistance is modified due to smoking, use of dentures, hyperglycemia, or other factors. The major contributing factors that predispose patients with IDDM to clinical infection appear to be current cigarette smoking, use of partial or complete dentures, and poor glycemic control. Strict glycemic control and abstinence from smoking may reduce the risk of candidiasis in patients with IDDM. [5]

Glycosylated hemoglobin concentrations above 12% were significantly associated with oral yeast infection, which suggests that fungal infections of mucous membranes may only be significantly associated with diabetes in patients with a longer history of hyperglycemia. Being diabetic in itself may not place a person at increased risk of fungal infection, unless diabetic control is very poor, as evidenced by glycosylated hemoglobin concentrations of more than 12%. [12] The absence of clinical manifestations of candidiasis in our study can be attributed to good glycemic control and absence of factors like smoking, denture wearing and a relatively younger age of the patients.

Diabetics are also known to manifest other oral soft tissue pathologies like oral lichen planus, asymptomatic salivary gland enlargement, recurrent aphthous stomatitis [13].

In our study the oral soft tissue pathologies were more prevalent among males than females. The commonest noncandidal soft tissue pathologies seen were fissured tongue, gingivitis, migratory glossitis, and irritation fibroma. In our study we found no prevalence of lichen planus in either the diabetic or the nondiabetic population.

Fissured tongue, including generalized plication and a double fissure running longitudinally along the dorsum of the tongue, has been reported to be more prevalent in persons with IDDM. It has been estimated, however, that the prevalence of fissured tongue in the general population can range up to 5%. The

pathogenesis of fissured tongue is considered to be a genetically determined developmental variant, a manifestation of aging or changes in the oral environment. [14]

In our study, a 17% prevalence of fissured tongue was seen in the diabetic population compared to 8% in the nondiabetics. It was found to be more prevalent among females. Its presence was significantly related to the older subjects who had a longer duration of IDDM.

Benign migratory glossitis is shown to have a higher incidence in patients with IDDM than in the general population. **[15]** In our study benign migratory glossitis was found to occur in 4% of the type 1 diabetics when compared to 2% in the control subjects. These results suggest that benign migratory glossitis may be linked to diabetes mellitus and that further investigation of this association is warranted.

Type 1 diabetic patients have a higher prevalence of oral traumatic ulcers and irritation fibromas than do nondiabetic control subjects. These findings may be related to altered wound healing patterns in these patients. [1] However study by Jorda LM did not reveal any association between diabetes mellitus and oral soft tissue lesions. [16]

In our study group the prevalence of traumatic ulcer and irritation fibroma in the type 1 diabetics was 3% and 4% respectively compared to 1% each in the control group. This shows that the prevalence of these soft tissue lesions was higher in diabetics when compared to nondiabetics.

Recurrent aphthous stomatitis has also been reported in patients with diabetes mellitus. Not all study results have shown this association and this is a relatively common disorder that is often observed in patients who donot have diabetes. [7, 17] Our study did not show higher prevalence of this lesion in type 1 diabetics.

Persistent poor glycemic control has been associated with the incidence and progression of diabetes related complications including gingivitis. **[7]** In our study group diabetics had a prevalence of gingivitis in 14% while the nondiabetics had a prevalence of 20% which was statistically insignificant. Gingivitis was found to be more prevalent among males compared to females.

Morphological changes such as sialadenosis is said to be present in diabetics (Russotto 1981) [18]. However, in all our patients no such enlargement was observed.

In the present study subjects with diabetes manifested a significantly reduced stimulated salivary flow and a negative candida carrier state compared with controls. No candida lesion was identified in the diabetics and they manifested a greater prevalence of fissured tongue. Other soft tissue abnormalities were not found to be prevalent in the group of subjects with type 1 diabetes.

CONCLUSION

It is difficult to establish comparison among studies due to diversity in patient selection criteria and study designs involved. However due to the smaller sample size the results obtained in this study may not be definitive. The results of our study need to be confirmed in longer longitudinal population studies by more advanced methods.

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