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Evaluation of Salivary Flow Rate in Diabetic Patients on Sulfonylurea Drugs and Biguanide Drugs.

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Abstract: The aim of the study was to evaluate the salivary flow rate in diabetic patients under two different and commonly used medications- the sulfonylurea derivatives and the biguanides. The study comprises of 3 groups, of which group 1 involves 74 diabetic petients under sulfonylurea derivatives drug and group 2 involves 74 diabetic patients under biguanide drugs. Group 3 serves as the control group with 74 healthy individuals belonging to the same age group. Both the unstimulated and stimulated saliva was collected for a duration of 15 mins each in a glass beaker, allowed to stand for some time and the liquid component alone measured using a sterile syringe. The statistics indicates relevant decrease in salivary flow in well controlled diabetic patients and also decrease in unstimulated salivary flow in patients who are under long term biguanide drug intake.
Keywords: salivary flow rate, diabetic patients, sufonylurea derivatives, biguanides.

Introduction:

The average life expectancy of an Indian has gone up from 32 years in 1951 to around 60 years in 1993. Better health care facilities and improvement in standard of living have been the key factors responsible for the increase in life expectancy.[1] Studies have revealed that the most common health-related problem among elderly Indians are hypertension, arthritis, diabetes, and constipation.[2] Several of these diseases and the medications used for them can cause reduction in the salivary flow.[3,4]

Dental care has been considered a part of primary health care.[5] Saliva is found to be the most important component in maintaining the normal form and function of the oral cavity. Normal salivary flow or adequate amount of saliva is very well associated with the wellness and better maintenance of the oral cavity. On an average, a person produces at least 500 mL of saliva over a 24-hour period. Salivary flow rates vary considerably depending on the demand or the current physiologic status of the patient. The unstimulated/resting flow rate is 0.3 mL/min, whereas the flow rate during sleep is 0.1 mL/min; during eating or chewing, it increases to 4.0 to 5.0 L/min.[6]

Xerostomia, or dry mouth, is the abnormal reduction of saliva and can be a symptom of certain diseases or be an adverse effect of certain medications. Xerostomia, is the most common adverse drug-related effect in the oral cavity.[6]

Reduced salivary flow or xerostomia is associated with oral dryness, taste loss, dysphagia, increased dental caries, and periodontal disease, ultimately deteriorating the quality of life.[3] Adequate amounts of saliva are very important and essential also to denture wearers. Wearing complete dentures can be an extremely uncomfortable experience for the people with Xerostomia. Dentures stay in place comfortably and in a stabilized

manner by development of an intimate interface between denture surfaces and the soft tissues they rest upon. Presence of adequate amounts of saliva within this denture/tissue interface is essential. Without enough saliva, a denture will inadequately adhere to tissues, partly through loss of suction.

Various treatment modalities have been suggested in the literature to overcome the problem of xerostomia in complete denture patients. Incorporating reservoirs containing salivary substitutes, into dentures, is one of these treatment modalities.[7] However, this is a rehabilitation procedure and could be overcome by a phase1- prevention procedure.

It is natural phenomenon for the salivary flow rate to decrease along with aging. Among the elderly people, who are edentulous and wearing dentures, instability of denture was a common complaint of patients who are diabetic. Saliva secretion might be more affected by xerogenic drugs and autonomic nervous dysfunction in patients with non-insulin-dependent diabetes than in nondiabetic control subjects.[8] This led to a question whether different types of oral hypoglycemic drugs has different effects on saliva.

Meurman *et al.* studied the flow rate and organic constituents of whole saliva in relation to autonomic nervous function in patients with non-insulin dependent diabetes. They found no difference in flow rate between the patients with diabetes and the control subjects. They concluded that the saliva secretion might be more affected by xerogenic drugs and autonomic nervous dysfunction in patients with non-insulin-dependent diabetes than in nondiabetic control subjects.[8]

Dodds, Yeh and Johnson conducted a study to determine whether saliva output and composition are altered in type 2 diabetes mellitus by comparison with a healthy, non-medicated control group, and also a group of hypertensives. They finally arrived at a result that both diabetic and hypertensive subjects had reduced output of both stimulated and unstimulated submandibular/sublingual saliva.[10]

Cristina de Lima D *et al* compared the diabetic and non-diabetic subjects wearing complete dentures with regard to salivay flow, salivary buffering capacity, denture retention and oral mucosal lesions. Within the limitations of this study, no significant differences were observed in salivary flow, denture retention or oral lesions in diabetic and non-diabetic subjects.[11] the controversy present between these two studies has drawn interest to start this study.

Bakianian vazir *et al.* compared the salivary flow rate in diabetic patients with healthy controls. They collected the saliva from the subjects by Navazesh method.[12] The results concluded that the salivary flow rate was significantly lower in diabetic patients.[13]

In a recent study conducted by shetty *et al*, it has been indicated that the severity of the xerostomia increases among the elderly due to a synergistic effect when taking multiple medications. Their study also concluded that oral hypoglycemic drugs causes xerostomia.[14]

The literature gives enough results to conclude that oral hypoglycemics induces xerostomia or dry mouth. But there is no sufficient information about each category of drugs and their action on salivary flow. As saliva is an important constituent of oral cavity, we are interested in finding out in detail about the individual drugs which was not done previously.

Materials and Methods:

The purpose of this experimental study is to evaluate both the stimulated and unstimulated salivary flow rate in diabetic patients under two different types of medication. The study consists of two groups and a control group.

Group 1:

74 type-2 diabetic patients under sulfonylurea medication and within the age group of 35 to 60 years.

Group 2:

74 type-2 diabetic patients under biguanide medication and also within the same age group of 35 to 60

years.

Control Group:

74 subjects within the age group of 35 to 60, without diabetes and should not be under any xerogenic medications like anti-hypertensives.

Inclusion Criteria:

1. Age limit falls between 35 to 60 years for all the three groups.
2. HbA1c levels measured before study.
3. Diabetic patients should be under medication within a range of 3-5 years.

Exclusion Criteria:

1. Patients who had undergone salivary gland surgery.
2. Subjects who are under any type of xerogenic medications.
3. Type-1 diabetic patients.

Collection of saliva was carried out in a ventilated and well illuminated room. Test was carried out in the mid-morning between 9:00am and 11:00am after one or two hours after the last food intake.[9] The participants were allowed to rest for 5 min, with their eyes closed, remaining comfortably seated, with their arms and their heads lowered and facing slightly forwards between their arms. Before collection, the participants rinsed their mouth with water. Then, after swallowing all the saliva present in the mouth, they were instructed to allow new saliva to accumulate in the mouth and to expectorate it into a receptacle.

The stimulated whole saliva collection was done 15 to 20 minutes after the collection of unstimulated whole saliva. The stimulus was a drop of lemon juice applied to the tongue about once in a minute throughout the 15 minutes collection period. The total saliva collected was aspirated from the collection receptacle with a disposable 10mL sterile syringe. The amount of saliva in mL, divided by the time duration of the collection was recorded as the mean salivary flow rate. Only the liquid component of the saliva, not the foam, was measured. The data obtained was then submitted to statistical evaluation.

Observations and Results:

The mean and standard deviation is shown in table 1.

Table 1: Mean and standard deviation of unstimulated saliva and stimulated saliva flow

		US1	SS1	US2	SS2	US3	SS3
N	Valid	74	74	74	74	74	74
Mean		.22	.95	.23	.99	.72	1.32
Std. Deviation		.150	.260	.163	.315	.209	.211

US1- group 1 unstimulated salivary flow
SS1- group 1 stimulated salivary flow
US2- group 2 unstimulated salivary flow
SS2- group 2 stimulated salivary flow
US3- group 3 unstimulated salivary flow
SS3- group 3 stimulated salivary flow

In table 2, the ANOVA test shows that there is high significance value ($P<0.001$) in the unstimulated saliva and stimulated saliva in both group1 and group2.

Table 2: ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
US	Between Groups	12.023	2	6.011	194.047	.000
	Within Groups	6.784	219	.031		
	Total	18.807	221			
SS	Between Groups	6.372	2	3.186	45.313	.000
	Within Groups	15.399	219	.070		
	Total	21.771	221			

US- unstimualted salivary flow
SS- stimulated salivary flow

During the post hoc multiple comparison test- bonferroni (table 3), the statistics indicates higher significant value (P<0.001) between group 3 i.e., the control group to group 1 and also between the control group to group 2.

Table 3: Post Hoc multiple comparison test – Bonferroni

	Dependent Variable	(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig.
US	Bonferroni	1	2	-.010	.029	1.000
			3	-.499*	.029	.000
		2	1	.010	.029	1.000
			3	-.488*	.029	.000
		3	1	.499*	.029	.000
			2	.488*	.029	.000
SS	Bonferroni	1	2	-.040	.044	1.000
			3	-.378*	.044	.000
		2	1	.040	.044	1.000
			3	-.338*	.044	.000
		3	1	.378*	.044	.000
			2	.338*	.044	.000

*. The mean difference is significant at the 0.05 level.

During the non-parametric comparison of unstimulated saliva of group 1 to time duration of patient drug intake, there is a negative correlation (table 4)

Table 4: correlation between the unstimulated salivary flow rate to time period of group 1 type of drug intake by the patient.

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Interval by Interval	Pearson's R	-.092	.105	-.788	.433[c]
N of Valid Cases		74			

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis.
c. Based on normal approximation.

During the non-parametric comparison of stimulated saliva of group 1 to time duration of patient drug intake, there is a negative correlation (table 5).

Table 5: correlation between the stimulated salivary flow rate to time period of group 1 type of drug intake by the patient.

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Interval by Interval	Pearson's R	-.003	.113	-.024	.981[c]
N of Valid Cases		74			

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis.
c. Based on normal approximation.

During non-parametric comparison of unstimulated saliva of group 2 to time duration of patient drug intake, there is a positive correlation (table 6).

Table 6: correlation between the unstimulated salivary flow rate to time period of group 2 type of drug intake by the patient.

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Interval by					
Interval	Pearson's R	.164	.108	1.414	.162[c]
N of Valid Cases	74				

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis.
c. Based on normal approximation.

During the non-parametric comparison of stimulated saliva to time duration of patient drug intake, there is a negative correlation (table 7).

Table 7: correlation between the stimulated salivary flow rate to time period of group 2 type of drug intake by the patient.

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Interval by					
Interval	Pearson's R	-.070	.114	-.593	.555[c]
N of Valid Cases	74				

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis.
c. Based on normal approximation.

Discussion:

Xerostomia, or dry mouth, is the abnormal reduction of saliva and can be a symptom of certain diseases or be an adverse effect of certain medications. Xerostomia, is the most common adverse drug-related effect in

the oral cavity.[6] xerostomia is a subjective feeling, characterized by dryness of mouth or reduced salivary flow. Saliva, is considered important in the field of dentistry. Normal salivary flow helps maintain the normal function of oral cavity. Altered salivary flow affects its functions in many ways. The role of saliva in this study focuses on its ability to hold the denture in position. Saliva acts as an interface between the denture and the mucosa. Previous studies conducted by Meurman *et al.* and Bakianian vazir *et al.* have concluded that diabetic patients have a reduced salivary flow compared to non-diabetic individuals and there was a question left behind stating that if this effect can be caused due to the diabetic medications.[8,13] This current study also indicates and in accordance with the earlier conducted studies that there is a highly significant ($P<0.001$) reduction of both stimulated and unstimulated saliva in diabetic individuals in comparison to non-diabetic individuals belonging to the same age group. The decreased salivary flow rate in the present study also indicates a different view from earlier conducted studies that these patients are diabetic under long term medications and their HbA1c values indicates good to fair control. The present study also indicates that there is a decrease in the unstimulated salivary flow rate in patients who are under long term biguanides medication. This particular finding was in accordance with the study conducted by bergdahl *et al*, that drugs or medications do cause decreased unstimulated salivary flow.[15] Although the current study indicated decreased salivary flow in a blood glucose controlled diabetic patient and also decrease in the unstimulated saliva in the biguanide drug intake group, the follow up and review of the current study was for a short period. This could be the possible limitation of the study. To identify a greater impact on saliva and xerostomia caused by anti diabetic drugs, long term studies, follow-ups and reviews are needed.

Conclusions:

Xerostomia has been associated with lot of hypertensive , anti-depressant, anti epileptic medications but this study opens a new window of thinking that even the anti diabetic drugs causes xerostomia. Also the long term intake of biguanide drugs causes decrease in unstimulated salivary flow rate compared to sulfonylurea derivative drugs.

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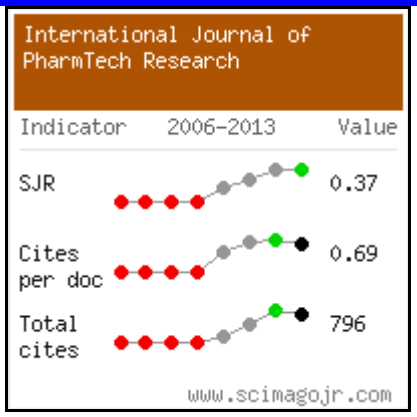

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