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Salivary flow and xerostomia in patients with type 2 diabetes

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Background: Saliva is secreted by the major and minor salivary glands. There are a number of physiological factors that can reduce this secretion such as age, sex, body weight, number of teeth present in the mouth or time of day. This decrease may also be caused by the use of certain drugs, radiotherapy for head and neck cancer, chronic rheumatic diseases such as Sjögren's syndrome and other systemic disorders such as diabetes mellitus (DM). Objective of this study was to investigate the effect of type 2 DM on salivary secretion and its relation to the sensation of xerostomia.

Methods: Forty-seven patients with type 2 DM and 46 healthy individuals, aged 40-80, participated in the study. Samples of saliva were collected, at rest and after stimulation, at baseline and after the administration of a meal. A questionnaire of 10 items was used to define the patients' sensations of xerostomia. For statistical analysis, the Mann-Whitney test was used to assess the difference in salivary flow between the two groups and the relationship between the response to each of the questions and salivary flow levels. The degree of the patients' sensation of xerostomia was analysed by the Fisher test.

Results and Conclusions: There was a significant decrease in total saliva levels at rest in patients with type 2 DM compared to the control group. The study group also experienced higher levels of dryness at night and on waking as well as a greater sensation of lingual burning compared to the control group.

KEYWORDS
diabetes mellitus type 2, saliva, xerostomia

1 | INTRODUCTION

Saliva is a body fluid composed 99% by water and 1% by organic and inorganic molecules. Daily salivary secretion varies widely between 500 mL and 1 L. There are a number of physiological situations that can reduce this secretion such as age, sex, body weight, number of teeth present in the mouth or time of day.[1] This decrease may also be caused by the use of certain drugs,[2] radiotherapy for head and neck cancer, certain chronic rheumatic diseases such as Sjögren's syndrome and other systemic disorders such as diabetes mellitus (DM).[3]

Prolonged hyperglycaemia, which is a characteristic of DM, besides generating systemic changes, can alter the function of the salivary glands and may cause changes in the composition and volume of secreted saliva.[3] Salivary gland hypofunction may lead to alterations at oral mucosa level such as increased glucose and mucin concentration, decreased production of antimicrobial substances, absence of the sensation of taste, halitosis, an increase in exfoliated cells and pathogens, saburral tongue, periodontal disease, caries, delayed healing of wounds and a tendency to develop oral mucosal diseases, such as oral candidiasis or lichen planus.[4] In addition, salivary gland hypofunction can cause problems for chewing, swallowing and lubrication leading to an inadequate diet and poor quality of life.[4]

Diabetic patients may suffer from xerostomia and salivary gland hypofunction,[5,6] which may be due to polyuria or alterations in the basement membrane of the salivary glands.[7] Xerostomia is defined as the subjective sensation of having a dry mouth,[8] but when we observe an objective reduction in output of saliva the condition is

referred to as salivary gland hypofunction.[8,9] Xerostomia varies among individuals and usually does not concur with objectively decreased values of salivary flow. However, when salivary flow is reduced by half, the individual experiences dry mouth.[3] Around 10%-30% of patients with DM experience xerostomia, with a decreased production of saliva.[10]

This study investigates the possible alterations of salivary flow in diabetic patients, and its relationship with the sensation of xerostomia, to investigate whether hyperglycaemia can negatively affect the functioning of the salivary gland.

2 | MATERIALS AND METHODS

2.1 | Study design and patient selection

A prospective, randomised study of cases and controls was carried out at the University Hospital Dr. Peset de Valencia (Spain). Randomisation was used to establish which patients were included in the study and which were not. The benefits of the introduction of a randomisation in the selection of cases for this study are: to eliminate the selection bias, to balance the groups with respect to many known and unknown confounding or prognostic variables and to provide a basis for the statistical methods used in analysing the data. The command "echo $ [RANDOM% 2 + 1]" in the MAC OSX operating system was used for this purpose. This command generates random numbers, assigning the value 1 or 2 to each participant. Patients who were assigned the value 1 were included in the study, the rest were discarded.

The experimental group consisted of 47 patients with type 2 DM, in care at the hospital while the control group consisted of 46 healthy individuals, with a mean age of 61.02 ± 6.01 and 59.43 ± 5.20 years, respectively. The diabetic group consisted of 19 men (40.4%) and 28 women (59.6%), the control group of 18 males (39.1%) and 28 females (60.9%). Type 2 diabetes was diagnosed according to American Diabetes Association.[11] The study was approved by the Clinical Research Ethics Committee of the hospital (code 09/093), following the principles of Helsinki for clinical trials in humans.

Consecutive subjects in care at the hospital were selected before going through the inclusion/exclusion criteria. Patients in both groups had to comply with the inclusion criteria: to be between the ages of 40 and 80, not to be smokers, to have at least 10 teeth. Women could not participate if pregnant or breastfeeding. Patients with decompensated systemic diseases like cardiac, inflammatory, hepatic, thyroid or renal alterations were excluded. Individuals with DM had to have HbA1c levels at ≤8% and take oral anti-diabetic therapy. The control group were healthy individuals, without diabetes or glucose intolerance, matched by age and sex with the diabetic group. They voluntarily participated in the study after signing an informed consent form.

2.2 | Saliva samples collection

On the day of the study, from 9 to 11 AM, patients were asked to come to the hospital with an empty stomach that is not having eaten for at least 10 hours before and without having performed any form of oral hygiene in the two hours previous to the study. After completing their clinical history, the patients were asked to rinse their mouths with distilled water. Subsequently, samples of total saliva, both at rest and after stimulation, were collected. Participants were then asked to eat a test meal of "Nestlé Resource® Energy" (a nutritional supplement: 15% protein, 55% carbohydrate and 30% fat), and after 120 minutes, a new sample of resting salivary flow rate (RSFR) and stimulated salivary flow rate (SSFR) was collected. RSFR was collected using a drainage technique which lasted 5 minutes by pouring it into a glass funnel which was connected to a test tube, which measured the results in mL/min. The saliva collected in the two minutes prior to initiation was discarded. SSFR was collected in the same manner by stimulating secretion by chewing a paraffin tablet (Paraffin Pellets from Ivoclar Vivadent, Liechtenstein) during the test, which again lasted 5 minutes.

2.3 | Xerostomia questionnaire

A questionnaire of 10 items relating to the sensation of xerostomia was employed,[12] seven of the items were adapted according to Fox's 1987 criteria,[13] which states that participates need to answer positively or negatively (see Table 1).In addition, based on Fox's criteria, if a patient responds positively to one or more of question numbers # 1, 2, 3 or 4, they are classified as a patient with xerostomia (Fox Summary).[6,13]

2.4 | Result variables

The levels of total saliva at rest and after stimulation in both groups were analysed while the participants were fasting as well as when they were in a postprandial state (2 hours). In addition, the sensation of xerostomia in these patients was analysed by a 10-item questionnaire.

2.5 | Statistic analysis

The description of the quantitative variables was estimated by calculating the mean and the standard deviation of each group as an

TABLE 1 Dodds xerostomia questionnaire 1997[12]

1-Do you feel your mouth dry when you eat?[a]
2-Do you have difficulty swallowing food?[a]
3-Do you need to drink to eat?[a]
4-Do you feel that the amount of saliva in your mouth is too small most of the time?
5-Do you feel dryness in your mouth at night or when you get up?[a]
6-Do you have dryness in your mouth at other times of the day?[a]
7-Do you take chewing gum or candy to improve your sense of dry mouth?[a]
8-Do you wake up during the night to drink water?
9-Do you have problems to taste food?
10-Do you have a burning sensation on your tongue?

[a]Adapted according to Fox's criteria.[26]

element to report on the dispersion of the sample, obtaining the absolute and relative frequencies for the categorical variables. The Mann-Whitney test was used to study the differences between the mean saliva levels between the groups and to study the association of each of the questions related to xerostomia with flow levels. In the case of categorical variables, their dependence was evaluated with the chi-squared or Fisher test, depending on whether or not they were 2 × 2 tables.

3 | RESULTS

There was a decrease in salivary flow levels, both basal and postprandial, in the group of patients with DM compared to the control group, although it was only significant in the case of basal RSFR ($P = .019$) and the mean values were 0.18 ± 0.16 mL/min and 0.24 ± 0.17 mL/min, respectively (Table 2). Diabetic patients presented greater dryness at night or on waking, as well as a sensation of increased burning of the tongue. As for the general sensation of xerostomia (Fox's summary), we found that it was somewhat greater in diabetic patients, in fact 13 patients with DM reported xerostomia, compared to only 6 in the control group, although the differences were not significant ($P = .122$) (Table 3).

In both the diabetic group and the control group, a decrease in basal RSFR levels was observed in patients with xerostomia. The same finding was observed with basal SSFR levels in both groups. In addition, it was found that there was a decrease in saliva rates in patients who responded positively to questions 1, 4, 5, 6 and 8 in the xerostomia questionnaire.

4 | DISCUSSION

Salivary flow levels in diabetic patients type 2 DM can cause alterations in the immune, cardiovascular, ocular and renal systems, and the salivary glands may be affected either directly or indirectly.[14]

In our study, we observed a decrease in both basal and postprandial salivary flow levels in the DM group, confirming some previous results,[6,14-17] although only significant differences were found in the case of basal RSFR. This decrease may be due to a variety of causes such as fatty infiltration of the salivary glands, the effect of polyuria dehydration, micro-vascular disease, local inflammation and irritation of the oral cavity, infections, metabolic disorders and neuropathies affecting salivary glands of these patients.[18] However, there are authors who did not find these differences between patients with DM and the control group,[19-22] possibly due to the fact that they had different inclusion criteria. Unlike our study, some of them included patients treated with xerostomising medication, generating a bias that makes it difficult to compare the two groups.[21]

TABLE 2 Salivary flow levels according to the existence or not of diabetic pathology

Levels of salival flow	Diabetic	Controls	*P*-value (MW)
Basal RSFR (mL/min ± DE)	0.18 ± 0.16	0.24 ± 0.17	.019*
Basal SSFR (mL/min ± DE)	0.88 ± 0.63	1,04 ± 0.64	.126
RSFR**120** (mL/min ± DE)	0.26 ± 0.22	0,29 ± 0.18	.242
SSFR **120** (mL/min ± DE)	0.89 ± 0.64	1,09 ± 0.64	.074

DM, Diabetes mellitus; DE, Standard deviation; basal RSFR, basal resting salivary flow rate; basal SSFR, basal stimulated salivary flow rate; RSFR120, postprandial resting salivary flow rate; SSFR120, postprandial stimulated salivary flow rate; MW, Mann-Whitney.
*$P < .05$.

In addition, qualitative changes have been observed in saliva with alterations in total proteins, lysozyme, peroxidases, electrolytes, amylase and IgA.[14,16,23,24] While some studies showed an increase in total protein, glucose, potassium and sodium levels, with a decrease in calcium levels,[14] other studies only observed an increase in salivary glucose levels.[24] Differences in composition and volume of the secreted saliva can be due to different factors such as the analysis of different types of saliva (stimulated or non-stimulated), the degree of the diabetic disease, the degree of metabolic control, the technique of saliva collection and the use of xerostomising medication which makes it difficult to compare the various studies.[16]

4.1 | Xerostomia

In the diabetic patients studied, we found a greater sensation of dryness of the mouth during the night and on waking in the morning than the control group. These data coincide with the phases of physiological secretion of saliva: increased salivation, hence less discomfort during the day and decreased salivation and more discomfort at night. This could be related to a greater lack of stimuli and to the presence of a certain degree of dehydration. In addition, the diabetic patients reported a burning sensation on the tongue, which could be related to a higher degree of irritation of the lingual mucosa.[20]

The percentage of patients with DM affected by xerostomia differs from one study to another. Our study showed similarities with the study by Arrieta et al[25] which also showed that 26.3% of DM patients experienced xerostomia, although in this case the study included patients with DM types 1 and 2. With the exception of the article by Vasconcelos et al[15] which reported xerostomia in 12.5% of diabetic patients, our study presented a lower percentage than most studies: we found that 27.7% of patients with DM had xerostomia, while studies such as Carda et al,[23] Sreebny et al[17] and Ben-Aryeh et al[26] reported a percentage of 76.4%, 43% and 31%, respectively. Some authors argue that the existence of a high prevalence of xerostomia in these patients could be due to the negative effect that the DM has on the sympathetic and parasympathetic nervous system, as well as the hormonal changes and the dehydration that usually affect these patients.[27] The low percentage of patients with xerostomia could be due to the small number of diabetic patients in the study. Limitations regarding the use of a non-validated questionnaire to assess xerostomia should be considered. In this study, the

TABLE 3 Summary of responses to xerostomia questions based on the existence or not of diabetic pathology

	Diabetics		Controls		
Questions	NO	SI	NO	SI	*P*-value (Fisher)
X1	41 (87.2%)	6 (12.8%)	45 (97.8%)	1 (2.2%)	.111
X2	46 (97.9%)	1 (2.1%)	43 (93.5%)	3 (6.5%)	.361
X3	44 (93.6%)	3 (6.4%)	45 (97.8%)	1 (2.2%)	.617
X4	36 (76.6%)	11 (23.4%)	41 (89.1%)	5 (10.9%)	.169
X5	19 (40.4%)	28 (59.6%)	31 (67.4%)	15 (32.6%)	.013*
X6	40 (85.1%)	7 (14.9%)	42 (91.3%)	4 (8.7%)	.523
X7	43 (91.5%)	4 (8.5%)	43 (93.5%)	3 (6.5%)	1.00
X8	33 (70.2%)	14 (29.8%)	39 (84.8%)	7 (15.2%)	.136
X9	47 (100%)	0 (0%)	45 (97.8%)	1 (2.2%)	.495
X10	39 (83%)	8 (17%)	45 (97.8%)	1 (2.2%)	.030*
Resum.Fox	34 (72.3%)	13 (27.7%)	40 (87%)	6 (13%)	.122

Resum. Fox: Fox's summary.
*$P < .05$.

questionnaire used was a non-validated modification of the Fox questionnaire which was also used in another study.[12]

Some authors have observed that patients with DM presented more problems when eating food, as well as a greater sensation of having a dry mouth when eating as well as problems when swallowing. However, in the last two cases, the results only had a trend towards statistical significance.[12]

4.2 | Relationship between the sensation of xerostomia and levels of salivary flow

In a recent systematic review by López-Pintor et al,[18] a decrease in salivary flow and an increase in the sensation of xerostomia in diabetic patients compared to non-diabetic patients were demonstrated.

However, although xerostomia usually results from a decrease in salivary flow rates, it may also occur at normal flow levels.[28] In a study of non-diabetic patients, it was observed that although there was a significant correlation between low total saliva levels and a sensation of xerostomia, it was also found that a high number of patients with abnormally low levels of salivary flow had no sensation of xerostomia, while others with normal flow did.[29]

Our results showed a relationship between low saliva levels and xerostomia sensation, both in the experimental and control group, in terms of basal saliva levels. Regarding the stimulated saliva, this relationship was also observed in the total sample and in the control group, with a great tendency in the diabetic group.

Similarly to our results, several authors confirmed this relationship,[17] stating that the sensation of having a dry mouth is a common ailment in diabetic patients and that its association is related to dehydration in these patients. They observed that 88% of patients with DM with xerostomia had a flow of unstimulated saliva of less than 0.1 mL/min.[17]

However, other studies disagree with this hypothesis,[5] proving that although there may be a decrease in the levels of saliva in the diabetic group, it does not necessarily imply an increase in the sensation of xerostomia. These data are explained by the fact that these patients may use compensatory mechanisms to improve their sensation of a dry mouth. In addition, changes in baroreceptors and alterations in the oral mucosa could contribute to the decrease in the sensation of xerostomia in the patients with DM.[30]

In conclusion, in type 2 DM, there is a decrease in resting saliva with a higher tendency to suffer from a burning sensation of the tongue. Oral dryness is greater at night or on waking than throughout the day. In our study, we observed a clear relationship between patients with xerostomia and those with low levels of salivary flow.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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