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Impact of Hyperglycemia on Xerostomia and Salivary Composition and Flow Rate of Adolescents with Type 1 Diabetes Mellitus

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1. Introduction

Xerostomia is defined as a subjective sensation of having a dry mouth (Fox et al., 1987) and is reported by the patient (Guggenheimer & Moore, 2003; Moore et al., 2001). The subjective feeling of dry mouth (xerostomia) is one of the oral manifestations of diabetes (Sreebny et al., 2006; von Bültzingslöwen et al., 2007). Xerostomia results from a reduction in saliva secretion, although it may occur in spite of the presence of a normal salivary flow rate (Guggenheimer & Moore, 2003; Scully, 2003). Altered saliva composition rather than the quantity of saliva may play a role in the induction of xerostomia (Anttila et al., 1998; Fox, 1996).

Type 1 diabetes mellitus (DM1) is a metabolic dysfunction characterized by hyperglycemia resulting from definitive deficiency in insulin secretion caused by autoimmune illness and genetic factors (ADA, 2004). The American Diabetes Association (ADA) reports that 75% of DM1 cases are diagnosed in persons under the age of 18 years (ADA, 2006). Glycemic control is fundamental to the management of diabetes and is associated with sustained decreased rates of microvascular (retinopathy and nephropathy) as well as neuropathic complications (ADA, 2008). Glycemic control has a modifying effect on the relation between dental caries and salivary factors in young patients (Syjälä et al., 2003).

Patients with DM1, particularly those who have poor glycemic control, may have decreased salivary flow rate (Guggenheimer & Moore, 2003). Many clinical problems develop in the presence of xerostomia, such as: difficulty in swallowing and speech, high susceptibility to oral infections (mainly candidiasis and dental caries), gingivitis and mucositis (Anttila et al., 1998). Furthermore, xerostomia was shown to have a negative impact on the quality of life of adolescents with DM1 (Busato et al., 2009).

The relationship among DM1, salivary composition and xerostomia has been widely investigated (Swanljung et al., 1992; Moore et al., 2001; López et al., 2003; Siudikiene et al., 2006; Siudikiene et al., 2008; Orbak et al., 2008). It has been found that most DM1 patients have salivary dysfunction as well as differences in biochemical salivary composition compared with healthy subjects (Swanljung et al., 1992; Moore et al., 2001; López et al., 2003; Siudikiene et al., 2006; Siudikiene et al., 2008; Orbak et al., 2008). Moreover, there is a lack of studies showing the relationship among hyperglycemia, xerostomia and salivary factors, especially in

adolescents with DM1. Thus, the aim of this study was to evaluate the association among hyperglycemia, xerostomia, salivary flow and composition of adolescents with DM1.

1.1 Materials and methods

This study was approved by the Research Ethics Committee of the Pontifical Catholic University of Paraná and by the Management of the Paraná Federal University Teaching Hospital. Patients and their parents or guardians were informed about the objective and the other aspects of the study and signed a Term of Independent Informed Consent.

1.1.1 Study groups and study design

A case-control epidemiologic study was performed on adolescents, allocated between two groups: control group, comprised of 51 non-diabetic subjects who were recruited from public high schools, and DM1 group, comprised of 51 adolescents with DM1, who receive follow-up at the Diabetes Outpatients Department of the Paraná Federal University Teaching Hospital. DM1 group and control group were paired regarding gender and age (14 – 19 years). DM1 diagnosis using the ADA (ADA, 2004) classification was established as a criterion for inclusion in DM1 group. The criterion for inclusion in control group was that of non-diabetic adolescents who had not used any medication for at least one month. The exclusion criteria used for both groups were: presence of systemic conditions that could influence salivary gland physiology, psychotropic drugs users, smokers, illicit drugs users or alcohol users (Busato et al., 2009).

1.1.2 Glycemic control

The results of postprandial capillary glucose (CG) tests performed at the time of saliva collection were recorded. Patients with good glycemic control were considered to be those with CG values of ≤ 130 mg/dL (DM1-A group), whereas hyperglycemic patients were considered to be those with CG values of > 130 mg/dL (DM1-B group) (ADA, 2006; 2008).

1.1.3 Xerostomia

Xerostomia was defined as a dry mouth sensation, reported by the subject. The subjects were asked if they had had a dry mouth sensation in the last six months (question A). If the answer was positive to xerostomia, they were also asked if it had occurred constantly during the last six months. Xerostomia was considered to exist if it had occurred daily during the six-month period. This evaluation was completed by the following questions: How would you describe the amount of saliva in your mouth? (question B). Do you have difficulty in swallowing food? (question C). Do you need to have something to drink in order to be able to swallow your food? (question D) (Carda et al., 2006).

Xerostomia was weighted according to three scales of perception: xerostomia 1 (dry mouth), when the answer to question A was "yes"; xerostomia 2, when there was a positive answer for question A and one other question (B, C or D); xerostomia 3, when there was a positive answer to question A and to two or more questions relating to xerostomia (B, C or D).

1.1.4 Saliva collection and treatment

Salivary flow was evaluated by means of stimulated saliva collection. The method used was that of mechanical masticatory stimulation, using a piece of sterile rubber tourniquet of a standardized size (1.5 cm), masticated continuously by the patient for six minutes. Saliva

produced during the first minute of stimulation was discarded. During the following five minutes, the patient expelled saliva into a sterilized universal collecting recipient that had been previously weighed using Marte® analytical scales, model AL 500 (São Paulo-SP/Brazil). The saliva was collected between 8 a.m. and 10 a.m. Stimulated saliva flow rate (SSFR) was evaluated by means of the gravimetric method and expressed in mL/min (Banderas-Tarabay et al., 1997).

The remaining saliva samples were centrifuged (3,000 g for 10 min). Total protein and calcium salivary concentrations were determined using a colorimetric method (LABTEST® kits/Vista Alegre-MG/Brazil). Amylase salivary concentrations were determined by a kinetic colorimetric method (LABTEST® kits/Vista Alegre-MG/Brazil). Urea salivary concentrations were determined by an enzymic colorimetric method (LABTEST® kits/Vista Alegre-MG/Brazil). Salivary glucose was analysed by an enzymic colorimetric method (BIOCLIN® kits/Belo Horizonte-MG/Brazil). The determination of the salivary concentrations was performed three times.

1.1.5 Statistical analysis

The data were analysed using SPSS version 15.0 for Windows. Normality analysis was performed using the Kolmogorov-Smirnov Test, and the Levene test was used to analyse variance homogeneity. The other tests used were Mann-Whitney test and Fisher's exact test considering statistically significant values ($p \leq 0.05$ and CI 95%).

2. Results and discussion

A total of 102 subjects were included in this study: 51 patients with DM1 (DM1 group) and 51 subjects without DM1 (control group). Twenty-seven subjects were female (52.9%) and 24 were male (47.1%) in each group (DM1 group and control group). Average age was 17 years (14-19, SD = 1.4) in both groups. In DM1 group, average CG was 200.5 mg/dL (SD = 108.09).

In the present study, hyperglycemia (CG > 130 mg/dL) was observed in 33 (65%) adolescents with DM1 (DM1-B group) while 18 (35%) showed good glycemic control (DM1-A group). DM1, regardless of glycemic control, was a risk factor for higher xerostomia prevalence and increased glucose salivary concentrations. Hyperglycemia was a risk factor for SSFR reduction and increased urea and calcium salivary concentrations.

The presence of xerostomia 1 (dry mouth) was indicated by 27/51 (53%) subjects in DM1 group, and 8/51 (16%) subjects in control group ($P < 0.001$) (Table 1). A total of 12 subjects (24%) stated the need to drink liquids during meals in DM1 group in contrast to 2 (4%) subjects in control group ($P = 0.004$). There were no significant differences between DM1 group and control group for the following questions: difficulty in swallowing food and amount of saliva perceived ($P > 0.05$). Only DM1 group subjects presented xerostomia 2 (n=10, 20%) and xerostomia 3 (n=5, 10%). There were significant differences between DM1 group and control group regarding xerostomia 2 ($P = 0.001$) and xerostomia 3 ($P = 0.028$) (Table 1).

Among well-controlled adolescents (DM1-A group), 11/18 (61%) subjects reported xerostomia 1, in contrast to 16/33 (48%) hyperglycemic adolescents (DM1-B group). There were significant differences between DM1-A and control group, and DM1-B and controls for

xerostomia 1 ($P < 0.05$) (Table 2). Table 2 shows the mean and the standard deviations of the salivary concentrations of total protein, amylase, urea, calcium and glucose in DM1, DM1-A, DM1-B and control groups. There were significant differences between DM1 and control groups for salivary concentrations of total protein ($P = 0.009$), calcium ($P = 0.001$), and glucose ($P = 0.021$). There were significant differences regarding total proteins ($P = 0.007$) and glucose ($P = 0.024$) salivary concentrations when DM1-A group was compared with control group. DM1-B group (adolescents with hyperglycemia) showed higher urea ($P = 0.042$), calcium ($P < 0.001$), and glucose ($P = 0.038$) salivary concentrations compared with controls.

Variables n (%)		DM1-group n = 51	Control group n = 51	*P* value
Xerostomia 1 (dry mouth)	Yes	27 (53)	8 (16)	<0.001 †
	No	24 (47)	43 (84)	
Need to drink	Yes	12 (24)	2 (4)	0.004 †
	No	39 (76)	49 (96)	
Amount of saliva perceived	Low	5 (10)	2 (4)	NS
	Normal	46 (90)	49 (96)	
Difficulty in swallowing	Yes	3 (6)	1 (2)	NS
	No	49 (94)	50 (98)	
Xerostomia 2	Yes	10 (20)	0 (0)	0.001 †
	No	41 (80)	51 (100)	
Xerostomia 3	Yes	5 (10)	0 (0)	0.028 †
	No	46 (90)	51 (100)	

DM1-group: adolescents with DM1, Control group: adolescents without DM1

† Fisher's exact test P ≤ 0.05, NS non-significant (P > 0.05)

Table 1. Characteristics of xerostomia of the studied population

Variables N (%) or mean (SD)	DM1-group n = 51	DM1-A n=18	DM1-B n=33	Control group n = 51	*P* value
Xerostomia 1					
Yes	27 (53)	11 (61)	16 (48)	8 (16)	<0.001[a c] †
No	24 (47)	7 (39)	17 (52)	43 (84)	0.001[b] †
SSFR (mL/min)	0.932 (0.537)	1.140 (0.688)	0.812 (0.361)	1.224 (0.577)	0.003[a] Ŧ NS[b] 0.002[c] Ŧ
Total Protein (mg/dL)	218 (386)	139 (67)	262 (460)	239 (144)	0.009[a] Ŧ 0.007[b] Ŧ NS[c]
Amylase (U/dL)	758 (33)	767 (35)	757 (31)	778 (9)	NS[a b c]
Urea (mmol/L)	5.340 (2.157)	4.662 (1.565)	5.769 (2.140)	4.957 (2.040)	NS[a b] 0.042[c] Ŧ
Calcium (mmol/L)	0.752 (0.496)	0.562 (0.366)	0.803 (0.515)	0.401(0.338)	0.001[a] Ŧ NS[b] <0.001[c] Ŧ
Glucose (mmol/L)	0.174 (0.183)	0.158 (0.154)	0.170 (0.189)	0.098 (0.115)	0.021[a] Ŧ 0.024[b] Ŧ 0.038[c] Ŧ

DM1-group: adolescents with DM1; DM1-A: adolescents with DM1 (CG ≤ 130mg/dL); DM1-B: adolescents with DM1 (CG > 130mg/dL); and Control group: adolescents without DM1
SSFR (stimulated salivary flow rate)
Ŧ Mann-Whitney U test, † Fisher's exact test, NS non-significant (P > 0.05)
[a] p value of DM1-group X control group; [b] p value of DM1-A X control group; and [c] p value of DM1-B X control group

Table 2. Salivary characteristics and xerostomia of the studied population

In the present study, xerostomia 1 prevalence was demonstrated in 27 (53%) adolescents with DM1 (DM1 group): 11 (61%) with good glycemic control and 16 (48%) with hyperglycemia, in contrast to 8 (16%) non-diabetes ones (control group) (Tables 1 and 2). Xerostomia was significantly associated with DM1 (Table 1) regardless of hyperglycemia (Table 2). Xerostomia 2 and xerostomia 3 only occurred in DM1 group, demonstrating that xerostomia is one of the oral manifestations of diabetes (Sreebny et a.l, 2006; von Bültzingslöwen et al., 2007). Xerostomia prevalence in elderly diabetic patients varies from

24.1% in patients with DM1 (Moore *et al* 2001) up to 76.4% in patients with type 2 DM (Carda et al., 2006). Moreover, there are limited accounts in the literature regarding the prevalence of xerostomia in adolescents with DM1, which makes direct comparisons between our study and other studies in adults difficult.

The need to drink liquids during meals was reported by 12 (24%) adolescents with DM1 and by 2 (4%) adolescents without diabetes (P = 0.004, Table 1). Nevertheless, in spite of this relationship between DM1 and "need to drink", it should be emphasized that family and individual habits may be related to this relationship. The habit of drinking juices, soft drinks or even water during meals is very common and frequently does not indicate a real necessity to drink in order to be able to swallow food. The clinical importance of the need to drink during meals among adolescents with DM1 needs to be further investigated in other studies.

In this study, average SSFR was 0.932 mL/min in DM1 group and 1.224 mL/min in control group (P = 0.003). In DM1-A group, average SSFR was 1.140 mL/min, presenting no significant difference compared with controls (P > 0.05) (Table 2). In the hyperglycemic subjects group (DM1-B), average SSFR was 0.812 mL/min. There was significant difference for SSFR between DM1-B and control groups (P = 0.002) (Table 2). Average SSFR values vary from 0.79 mL/min in children and adolescents with DM1 (Belazi et al., 1998) reaching 1.17 mL/min in adolescents with DM1 (Siudikiene et al., 2006). The latter value (Siudikiene et al., 2006) is similar to the average SSFR in well-controlled adolescents in the present study (DM1-A group, 1.140 mL/min, Table 2). The average SSFR value was significantly different between DM1 group (0.932 mL/min) and control group (1.224 mL/min), which is in consonance with previous studies with adolescents with DM1 (Siudikiene et al., 2006, 2008). In the present study, hyperglycemia was associated to a reduction in salivary flow (Table 2). This result agrees with a previous study, where it was suggested that it might be that the overall dehydration associated with hyperglycemia decreased the volume of saliva excreted (Karjalainen et al., 1996). Low salivary flow can influence increased caries experience in DM patients (Siudikiene et al., 2006, Márton et al., 2008). Furthermore, the subjective feeling of dry mouth (xerostomia) may result from a reduction in saliva secretion and was shown to have a negative impact on the quality of life of adolescents with DM1 (Busato et al., 2009).

Saliva contains immunological and non-immunological proteins with antibacterial properties (Humphrey & Williamson, 2001). In this study, good glycemic control (DM1-A group) was associated to a decrease in total proteins salivary concentration compared with controls. Conversely, there was no significant difference for salivary concentration of total proteins in the presence of hyperglycemia (DM1-B group) compared with non-diabetic subjects (control group). Moreover, amylase salivary concentration in adolescents with DM1 did not show significant differences compared with controls. Previous studies (Twetman et al., 2002; Mata et al., 2004; Carda et al., 2006; Moreira et al., 2009) have shown significant differences in total proteins salivary concentrations between subjects with and without DM1. Others studies are needed to further investigate the association of hypoglycemia with total proteins salivary concentrations in adolescents with DM1.

Salivary calcium concentration has a fundamental role in maintaining tooth integrity though the modulation of remineralization and demineralization (Humphrey & Williamson, 2001). In the present study, hyperglycemia was associated to an increase in salivary concentration

of calcium (Table 2), and calcium salivary concentration in DM1 group was significantly higher compared with that of control group, in consonance with a previous study (Mata et al., 2004).

3. Conclusion

In this study, the glucose salivary concentration was significantly higher in DM1, DM1-A and DM1-B groups when each one was compared with control group. Some studies (Belazi et al., 1998; López et al., 2003; Moreira et al., 2009) have shown this difference, whereas others studies (Swanljung et al., 1992; Carda et al., 2006) have not found difference in glucose salivary concentrations between subjects with and without DM1. The increased concentrations of glucose in the saliva of adolescents with DM1 may be important for controlling and monitoring the disease. It may possibly be related to blood glucose (Belazi et al., 1998; Iughetti et al., 1999; Mata et al., 2004).

There were no significant differences for urea salivary concentrations between adolescents with DM1 (DM1 group) and without DM1 (control group), which is in accordance with a previous study (Meurman et al., 1998) and contradicts others (López et al., 2003; Carda et al., 2006). Moreover, in the latters (López et al., 2003; Carda et al., 2006), subjects with DM1 showed higher urea salivary concentrations compared with controls.

In the present study, hyperglycemia was associated with an increased urea salivary concentration, with significant difference between DM1-B and control groups (Table 2). Hyperproteic diet and dysfunction of urea excretion due to renal failure may increase urea values in plasma and urine (Searcy et al., 1964). Future studies are needed to further investigate the relationship among the increased values of urea salivary concentration in adolescents with hyperglycemia, renal dysfunction and diet.

The significant difference in salivary composition and SSFR between adolescents with and without DM1 and the significantly higher xerostomia prevalence noted in adolescents who have DM1 may suggest an increased risk of dental caries and oral disease in DM1 patients. Furthermore, xerostomia has been shown to have a negative impact on the quality of life of adolescents with DM1 (Busato et al., 2009).

Moreover, there are limited accounts in the literature regarding the prevalence of hyperglycemia and its association with salivary composition, flow rate and xerostomia in adolescents with DM1, which makes direct comparisons between our study and other studies difficult.

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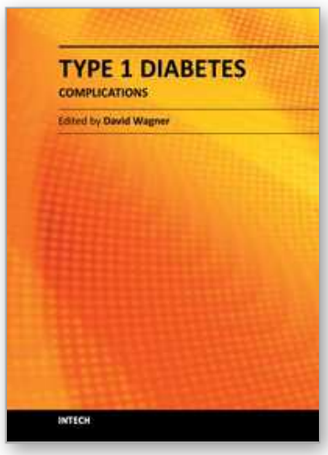

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