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IVANA MARIA SAES BUSATO

EFEITOS DO *DIABETES MELLITUS* TIPO 1 NA SAÚDE BUCAL EM ADOLESCENTES

CURITIBA

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Tese apresentada ao Programa de Pós-Graduação em Odontologia, Pontifícia Universidade Católica do Paraná, como parte dos requisitos para obtenção do título de Doutor em Odontologia – Área de Concentração em Estomatologia

Orientadora: Prof[a]. Dr[a]. Luciana Reis Azevedo Alanis

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“A alegria está na luta, na tentativa, no sofrimento envolvido e não na vitória propriamente dita”. **Mahatma Gandhi**

Nasci em 21 de abril de 1965, filha de Odete e Milton, e deste amor, *Deus* me deu a vida, em Dia de Tiradentes, e por destino, um dia abracei a odontologia como profissão. Nascer do ventre de uma mulher, minha mãe Odete, guerreira e sábia, que foi capaz de mudar a própria vida por seus filhos, que ama com a delicadeza da borboleta e luta como uma tigresa, agradecer é pouco, prefiro dizer: “eu te amo pela eternidade”; **dedico**.

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“ Se eu pudesse deixar algum presente à você, deixaria aceso o sentimento de amar a vida dos seres humanos. A consciência de aprender tudo o que foi ensinado pelo tempo a fora. Lembraria os erros que foram cometidos para que não mais se repetissem. A capacidade de escolher novos rumos. Deixaria para você, se pudesse, o respeito aquilo que é indispensável. Além do pão, o trabalho. Além do trabalho, a ação. E, quando tudo mais faltasse, um segredo: o de buscar no interior de si mesmo a resposta e a força para encontrar a saída” **Mahatma Gandhi**

SUMÁRIO

cont.

1.RESUMO

O objetivo deste estudo foi investigar os efeitos do *diabetes mellitus* tipo 1 (DM1) na saúde bucal de adolescentes. Estudo caso-controle de 102 adolescentes pareados por sexo e idade: grupo DM1, composto por 51 adolescentes com DM1 e grupo controle, composto por 51 adolescentes sem DM1. Indivíduos do grupo DM1 foram avaliados pelo tempo de DM1 e testes de hemoglobina glicada (GHb) e glicose capilar (GC). Foram avaliadas condições de saúde bucal: manifestações bucais, e índices CPOD e Periodontal Comunitário (IPC); e condições salivares: fluxo salivar estimulado (FSE), pH, capacidade tampão (CTS), concentrações salivares de proteínas totais, amilase, ureia, cálcio e glicose. A xerostomia foi detectada por questionário e o OHIP-14 foi utilizado para medir seu impacto na qualidade de vida (QOL). Foi realizada análise bivariada e regressão logística múltipla. A média de idade foi 17 anos (DP=1,4; 14-19); 27 adolescentes do sexo feminino e 24 do sexo masculino em ambos os grupos. O tempo médio de diagnóstico de DM1 foi 8,5 anos. A hiperglicemia (GC > 130 mg/dL) foi observada em 65% (n=33) dos adolescentes e o mau controle metabólico (GHb > 8,0%), em 67% (n=34). Um total de 53% (n=27) dos adolescentes do grupo DM1 e 16% (n=8) do grupo controle apresentou xerostomia ($p < 0,001$). Os valores médios de FSE foram 0,932 mL/min no grupo DM1 e 1,224 mL/min no grupo controle, com diferença significante entre grupos ($p = 0,003$). Na análise bivariada, houve diferença significante ($p \leq 0,05$) entre os grupos para xerostomia, Índice CPOD, IPC, prevalência de manifestações bucais, FSE, pH, CTS e concentrações salivares de proteínas totais, cálcio e glicose. Na regressão logística, houve significativa associação entre DM1 e xerostomia, e a QOL mostrou associação com xerostomia e experiência de cárie ($p \leq 0,05$). DM1 foi considerado fator de risco a xerostomia e a diminuição do FSE. Hiperglicemia e mau controle metabólico foram associados a diminuição do FSE. Hiperglicemia mostrou associação com aumento das concentrações salivares de uréia e cálcio. Experiência de cárie e xerostomia mostraram impacto negativo na QOL de adolescentes com DM1.

PALAVRAS-CHAVES: *diabetes mellitus* tipo 1, xerostomia, qualidade de vida, saliva, índice CPOD, OHIP-14, fluxo salivar, periodonto.

Effects of type 1 diabetes mellitus on oral health of adolescents

The purpose of this study was to investigate the effects of type 1 diabetes mellitus (DM1) on the oral health of adolescents. A cross-sectional study was performed with 102 adolescents paired regarding sex and age: DM1 group, comprised of 51 adolescents with DM1 and control group, comprised of 51 adolescents without DM1. In DM1 group, time of DM1 and metabolic control data were observed (glycosylated hemoglobin – GHb, capillary glucose - CG). The oral health conditions were assessed: DMFT Index and Community Periodontal Index (CPI), oral manifestations; as were the salivary conditions: stimulated salivary flow rate (SSFR), pH, buffer capacity (BC), total protein, amylase, urea, calcium and glucose salivary concentrations. Xerostomia was detected using a questionnaire and OHIP-14 was used to measure its impact on quality of life (QOL). Bivariate analysis and multiple logistic regression were performed. The average age was 17 years (SD=1.4; 14-19); 27 females and 24 males in both groups. The average time since DM1 diagnosis was 8.5 years. Hyperglycemia (GC > 130 mg/dL) was detected in 33 (65%) adolescents and 34 (67%) presented with poor metabolic control (GHb > 8.0%). A total of 27 (53%) adolescents in DM1 group and 8 (16%) in control group presented with xerostomia ($p < 0.001$). SSFR mean values were 0.932 mL/min in DM1 group and 1.224 mL/min in control group ($p = 0.003$). The bivariate analysis showed significant difference ($p \leq 0.05$) between the groups for xerostomia, DMFT index, CPI, prevalence of oral manifestations, SSFR, pH, BC and salivary concentrations of total proteins, calcium and glucose. The logistic regression showed significant association between DM1 and xerostomia, and QOL had association with xerostomia and caries experience ($p \leq 0.05$). DM1 was considered to be a risk factor for xerostomia and SSFR reduction. Hyperglycemia and poor metabolic control showed association with decrease in SSFR. Hyperglycemia had association with increase in urea and calcium salivary concentrations. Caries experience and xerostomia showed to have a negative impact on the QOL of adolescents with DM1.

Key words: diabetes mellitus, xerostomia, quality of life, saliva, DMF index, OHIP-14, salivary flow, periodontal.

3.INTRODUÇÃO

O *diabetes mellitus* tipo 1 (DM1) é uma disfunção metabólica caracterizada pela hiperglicemia resultante da deficiência definitiva na secreção de insulina, provocada por doença auto-imune e fatores genéticos (ADA, 2004). O relacionamento entre DM1 e condições de saúde bucal (MOORE *et al.* 2001; LÖPEZ *et al.* 2003; SWANLJUNG *et al.* 1992; GUGGENHEIMER *et al.* 2000; ARRIETA-BLANCO *et al.* 2003; AREN *et a.* 2003; BELAZI *et al.* 1998; ORBAK *et al.* 2008; SIUDIKIENE *et al.* 2008) e condições salivares (SWANLJUNG *et al.* 1992; BELAZI *et al.* 1998; AREN *et al.* 2003; LÓPEZ *et al.* 2003; SIUDIKIENE *et al.* 2006; SIUDIKIENE *et al.* 2008) tem sido amplamente investigado. A xerostomia (boca seca) é uma das manifestações bucais do DM1 (ARRIETA-BLANCO *et al.* 2003; von BÜLTZINGSTÖWEN *et al.* 2007).

Xerostomia significa uma sensação subjetiva de boca seca (FOX, 1987) e representa um sintoma relatado pelo paciente (MOORE *et al.,* 2001; GUGGENHEINER e MOORE, 2003). Xerostomia pode resultar da redução da secreção salivar ou ocorrer na presença de fluxo salivar normal (GUGGENHEINER e MOORE, 2003). Alterações na composição da saliva e na quantidade de saliva podem induzir a xerostomia (ANTTILA, KNUUTTILA, SAKKI, 1998).

Locker (1998) propôs um modelo conceitual da saúde bucal que avalia o impacto da mesma na qualidade de vida (QOL). É um modelo multidimensional para entender as doenças bucais e suas consequências. Em 1997, Slade (1997) estudou a possibilidade de avaliar este impacto por meio do *Oral Health Impact Profile* – OHIP -14 (14 questões), uma versão menor que o *Oral Health Impact Profile* – OHIP (49 questões), mantendo confiança, validade e precisão. A relação entre a QOL e a xerostomia vem sendo estudada em trabalhos recentes (LOCKER 2003; SANDBERG e WIKBLAD, 2003; THOMSON 2006; BAKER *et al.* 2007; BAKER 2007; BAKER *et al.* 2008).

A manutenção do controle metabólico em adolescentes com DM1 é um grande desafio para profissionais de saúde (SILVERSTEIN *et al.* 2005). Efeitos do controle glicêmico podem interferir na relação entre carie dental e fatores salivares em jovens com diabetes (SYJÄLÄ *et al* 2003). O inadequado controle metabólico pode resultar na hipofunção salivar em pacientes com diabetes (SIUDIKIENE *et al.* 2006; von

BÜLTZINGSTÖWEN *et al.* 2007). Redução de fluxo salivar causada pela hiperglicemia é característica do mau controle metabólico do DM1 (SIUDIKIENE *et al.* 2006).

A pesquisa objetivou analisar os efeitos do DM1 na saúde bucal em adolescentes, e com os seguintes objetivos específicos:

- ✓ prevalência de experiência de cárie dental pelo Índice CPOD
- ✓ avaliação do periodonto pelo Índice Peridontal Comunitário
- ✓ presença de xerostomia e manifestações bucais
- ✓ avaliar o impacto da xerostomia na QOL
- ✓ avaliar o fluxo salivar estimulado, pH e capacidade tampão da saliva
- ✓ concentrações salivares de ureia, glicose, cálcio, proteínas totais e amilase

A hipótese deste estudo é que a presença de DM1, as condições de saúde bucal e salivares influenciam na prevalência da xerostomia com impacto negativo na QOL de adolescentes.

O Artigo 1, com o título "*Impact of xerostomia on the quality of life of adolescents with type 1 diabetes mellitus"*, avaliou o impacto da xerostomia na qualidade de vida de adolescentes com DM1. Consistiu de um estudo epidemiológico transversal com amostra de 51 adolescentes com DM1, no qual foi realizada análise estatística bivariada. O artigo foi publicado no periódico *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 2009;108:376-382.*

"*Association between metabolic control and oral health in adolescents with type 1 diabetes mellitus"* é o título do artigo 2, que avaliou a relação entre o controle metabólico e a saúde bucal de adolescentes com DM1. Consistiu de estudo epidemiológico de caso-controle com 102 adolescentes, 51 com DM1 e 51 não-diabéticos. Foi realizada análise estatística bivariada entre os grupos. Em outubro de 2009, o artigo foi aceito para publicação no periódico *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology (on line).*

O artigo 3, com o título "Impacto da hiperglicemia na composição e fluxo salivar e na xerostomia de adolescentes com *diabetes mellitus* tipo 1", objetivou avaliar a hiperglicemia na composição salivar e xerostomia em adolescentes com DM1. Estudo epidemiológico de caso-controle com 102 adolescentes, 51 com DM1 e 51 não-diabéticos, no qual foi realizada análise estatística bivariada entre os grupos.

O Artigo 4, com o título “Xerostomia e qualidade de vida: condições de saúde bucal e salivares em adolescentes com *diabetes mellitus* tipo 1”, visou investigar a influência das condições de saúde bucal e salivares na prevalência da xerostomia e seu impacto na qualidade de vida de adolescentes com DM1. Estudo epidemiológico de caso-controle com 102 adolescentes, 51 com DM1 e 51 não-diabéticos, no qual foi realizada análise estatística bivariada entre os grupos e regressão logística múltipla.

“*Diabetes mellitus* tipo 1: fluxo salivar estimulado e características salivares em adolescentes” é o título do artigo 5. Estudo epidemiológico de *follow-up* com 32 adolescentes com DM1, avaliados em dois momentos, inicial e 15 meses depois, no qual foi realizada análise estatística bivariada entre os dois momentos.

Impact of xerostomia on the quality of life of adolescents with type 1 diabetes mellitus

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ABSTRACT

Objective. To evaluate the impact of xerostomia on the quality of life (QOL) of adolescents with type 1 diabetes mellitus (DM1).

Study design. The sample was comprised of 51 adolescents with DM1. Diabetic status was determined by glycosylated hemoglobin (HbG) and capillary glucose (CG) tests. Poor metabolic control was defined as HbG >8.0% and CG <90 mg/dL or >130 mg/dL. Measurement of salivary flow was performed by means of stimulated saliva collection. Xerostomia was detected by asking a question about the sensation of having “dry mouth,” and OHIP-14 was used to measure the impact of xerostomia on QOL.

Results. A total of 52.9% of subjects presented with xerostomia and 40.8% with hyposalivation. Significant differences between the subjects with and without xerostomia regarding metabolic control levels were not observed ($P > .05$). However, OHIP-14 scores were significantly different between the subjects with and without xerostomia ($P < .001$).

Conclusions. Xerostomia is frequent and has a negative impact on QOL of adolescents with DM1. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:376-82)**
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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.[1] The American Diabetes Association (ADA) reports that 75% of DM1 cases are diagnosed in persons under the age 18 years.[2] Adolescence is a period of biologic alterations and increased psychologic, emotional, and cognitive maturity. This stage of life is marked by increased independence from family members and the quest for social involvement with friends. For these reasons, patients with DM1 can lose adherence to treatment and monitoring of the disease.[3]

The subjective feeling of dry mouth (xerostomia) is one of the oral manifestations of DM,[4] and its prevalence varies from 24.1% in elderly DM1 patients[5] to 76.4% in elderly DM2 patients.[6] There are limited reports of the prevalence of xerostomia in adolescents with DM1. Xerostomia results from a reduction in saliva secretion, although it may occur in spite of the presence of a normal saliva flow rate.[7] Altered saliva composition rather than the quantity of saliva may play a role in the induction of xerostomia.[8] Patients with DM1, particularly those who have poor glycemic control, may have decreased salivary flow rate (SFR).[7,9]

In the presence of xerostomia, many clinical problems develop. These include mucosal dryness, difficulty in swallowing and speech, high susceptibility to oral infections (mainly candidiasis and dental caries) gingivitis, and mucositis.[8] It is important to periodically evaluate SFR in patients with xerostomia to treat the negative effects on oral health.[4,5]

Locker[10] proposed the identification and development of measures or indicators that are sensitive and valid in investigating clinical conditions and their relationship with impact on quality of life (QOL). In 1997, Slade[11] studied the possibility of reducing the number of items proposed by the Oral Health Impact Profile (OHIP; 49 items), and proposed a reduced version, OHIP-14 (14 items), maintaining confidence, validity, and accuracy. Since then, various studies have used this profile to evaluate the impact of oral health on QOL.[10-20]

There is increasing recognition of the impact of oral health on people's QOL, and this impact can be influenced by the presence of xerostomia. The relationship between QOL and xerostomia has been studied in recent research.[12-16,18,21-23] The aim of the present study was to evaluate the impact of xerostomia on the QOL of adolescents with DM1.

MATERIAL AND METHODS

Population

A transverse epidemiologic study was performed on adolescents aged 14 to 19 years with DM1, who receive follow-up at the Diabetes Outpatients Department of the Paraná Federal University Teaching Hospital. A total of 56 patients were considered for the sample. The diagnosis of DM1 using the ADA[1] classification was established as a criterion for inclusion in the sample. The exclusion criteria used for the sample were: presence of systemic conditions that could influence the salivary gland physiology, such as: hypothyroidism, obesity, cachexia, history of radiotherapy in the head and neck regions, and/or chemotherapeutic treatment in the preceding 3 months, psychotropic drug users, smokers, illicit drug users, or alcohol users. 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. This study was approved by the Research Ethics Committee of the Pontifícia Universidade Católica do Paraná and by the Management of the Paraná Federal University Teaching Hospital.

Evaluation of metabolic control

The results of glycosylated hemoglobin (HbG) tests performed < 3 months before saliva collection and the results of capillary glucose (CG) tests performed at the time of saliva collection were recorded. Patients with good metabolic control were considered to be those with HbG values of ≤ 8.0%, whereas poorly controlled patients were considered to be those with HbG values of > 8.0%. Capillary glucose values between 90 and 130 mg/dL characterized good glycemic control.[2]

Evaluation of xerostomia and hyposalivation

To determine the presence of xerostomia, patients were asked if they had a dry mouth during each day of the past 6 months. A positive response indicated xerostomia, for which these patients were asked 3 additional questions: How would you describe the amount of saliva in your mouth? Do you have difficulty in swallowing
food? Do you need to have something to drink to be able to swallow your food?[6]

Hyposalivation 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 6 minutes. Saliva produced during the first minute of stimulation was discarded. During the

subsequent 5 minutes, the patient expelled saliva into a sterilized universal collecting recipient that had been previously weighed using a Marte analytical scale, model AL 500 (São Paulo, 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.[24] SSFR values of > 0.7 mL/min were considered to represent normal saliva flow. SSFR values of ≤ 0.7 mL/min were considered to indicate hyposalivation. [25]

Evaluation of impact on QOL

Evaluation of the impact of xerostomia on QOL was performed using an OHIP-14 questionnaire.[10] The OHIP-14 was translated to Portuguese, maintaining the same psychometric properties as the instrument has in its original language.[19] Patients were asked to answer the question considering the previous 6-month period. In this study, OHIP-14 was evaluated according to the following dimensions: functional limitation, physical pain, psychologic discomfort, physical incapacity, psychologic incapacity, social incapacity, and social disadvantage. The answers were assessed using a Likerttype evaluation scale with 5 points: never = 0; rarely = 1; sometimes = 2; repeatedly = 3; always = 4. Replies stating "never" and "rarely" were considered as not having an impact on QOL. Replies stating "sometimes," "repeatedly," and "always" were considered as answers indicating a negative impact on QOL.

The standardized weighted method was used to calculate the impact of xerostomia on QOL.[19,20,26] To each question a weight was attributed.[20,26] The weight of each question was multiplied by the corresponding answer score (0-4). The final individual scoring enabled values between 0 and 28 to be obtained. In the sample studied, OHIP-14 mean value was calculated by the arithmetic mean among the final individual scores from the 51 adolescents. The higher the value was, the more negative was the impact of xerostomia on QOL.[19,20]

Statistical analysis

The data was analyzed using SPSS version 15.0 for Windows, considering xerostomia and hyposalivation to be dependent variables at 2 distinct moments of the evaluation. The independent variables evaluated were: gender, age, length of time DM1 had been diagnosed, HbG, CG, SSFR, and OHIP-14. Normality analysis was performed using the Kolmogorov-Smirnov test, and the Levene test was used to analyze variance homogeneity. The other tests used were Student *t*, Mann-Whitney, chi-squared, and Fisher exact,

considering statistically significant values ($p \leq .05$). The odds ratio (OR) was evaluated in relation to the dichotomic variables.

RESULTS

A total of 56 patients with DM1 were included in the study. However, 5 patients were excluded from the sample because of the presence of a systemic condition (hypothyroidism; n = 3) that could influence salivary gland physiology and antidepressant drug use (n= 2), leaving a total of 51 patients in the sample (Table I). Average age was 17.2 years (range 14-19, SD 1.36). Twenty-seven subjects were female (52.9%) and 24 were male (47.1%). Thirty subjects (58.8%) had been diagnosed as having DM1 for up to 9 years, and 21 (41.2%) had been diagnosed as having DM1 for over 10 years. Average CG was 200.46 mg/dL (range 47- 463, SD 108.09). One individual did not take this test at the time of saliva collection. Average HbG was 9.8% (range 5.7-15.3, SD 2.36). Four patients had not taken this test in the preceding 3 months.

OHIP-14 scores varied from 0 to 16 (SD 4.58) and were categorized as follows: 0 = without impact; 1-3 = low impact; 4-6 = medium impact; 7-10 = negative impact; 11-16 = high negative impact.[26] The average OHIP-14 score was 5.2, representing a medium impact of xerostomia on QOL. Table I shows the distribution of OHIP-14 scores, the mean, standard deviation, and range as well as percentage per category of impact.

The presence of xerostomia was indicated by 27 subjects (52.9%). A total of 5 patients (9.8%) stated having a low amount of saliva. Difficulty in swallowing food was related by 3 (5.9%) patients, and 12 (23.5%) stated the need to drink liquids during meals. Average SSFR was 0.917 mL/min (range 0.196-2.953, SD 0.54), which represented a normal SSFR. Two saliva samples were discarded because of problems with the method at the time of collection. Hyposalivation affected 20 patients (40.8%), and 29 (59.2%) had normal SSFR (Table I). When the impact of xerostomia on QOL was evaluated, taking xerostomia as a dependent variable, the OHIP-14 score was the only independent variable with significant difference ($P < .001$), between the subjects with (mean = 7) and without (mean = 2.71) xerostomia (Table II). Subjects with xerostomia (n = 8) showed more necessity to have something to drink to be able to swallow food compared with subjects without xerostomia (n = 4) (OR 2.11, 95% confidence interval 0.059-0.235; Table II).

When hyposalivation was analyzed as a dependent variable in relation to the other independent variables, there were no variables with significant differences between the

subjects with hyposalivation and those with normal SSFR. The OR results also showed that none of the independent variables presented clinical relevance in the studied population ($P > .05$). Table III shows the number of replies with and without negative impact per question in subjects with xerostomia. When the number of replies with negative impact was compared with the number of replies without impact, significant differences were observed for the questions involving social incapacity and social disadvantage ($P < .01$) as well as for functional limitation and physical incapacity ($P < .02$). Also, psychologic discomfort and psychologic incapacity ($P < .01$) as well as physical pain ($P < .05$) showed significant differences between the number of replies with and without negative impact in 1 question, respectively.

DISCUSSION

Because xerostomia is an oral manifestation of DM[4] and its presence can contribute to several clinical and social problems,[8] we set out to evaluate the relationships between diabetes control, salivary function, xerostomia, and OHIP-14 in adolescents with DM1. In the present evaluation of 51 patients, we found that a high percentage of individuals (52.9%) had xerostomia, although it did not present a relationship with hyposalivation. Xerostomia correlated with the need to drink and had a negative impact on QOL as measured by OHIP-14. However, neither duration of disease nor metabolic control of DM correlated with the presence or absence of xerostomia.

In this study, xerostomia was considered to be present if it occurred daily during the preceding 6 months. This evaluation was completed by 3 questions regarding the individual perception of the amount of saliva in his/her mouth, difficulty in swallowing food, and the need to drink something to be able to swallow food. In this study, xerostomia prevalence was demonstrated in 52.9% of adolescents with DM1, which is in consonance with the results of Sandberg et al.[27] (53%) for elderly patients with DM2. Xerostomia prevalence in elderly DM patients varies from 24.1% in patients with DM[15] to 44.4% in chronic renal patients with DM,[22] and reaching 76.4% in patients with DM2.[6] There are limited reports 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.

Xerostomia results from a reduction in saliva secretion, although it may occur in spite of the presence of a normal SFR.[7] In the present study, the average SSFR value (0.917 mL/min) was considered to represent a normal saliva flow (>0.7 mL/min),[25] in spite of 20 of

the adolescents (40.8%) presenting hyposalivation. This is in consonance with the study by Siudikiene et al.,[28] which found an average SSFR value of 1.17 mL/min when investigating SSFR in young people with DM1. Both studies showed that DM1 was not a conditioning factor of hyposalivation, in contrast to Chávez et al.,[29] who concluded that DM patients were vulnerable to hyposalivation. In the present study, hyposalivation did not present a relationship with xerostomia (p = .380; Table II). Ten out of 20 patients with hyposalivation (50%) complained of xerostomia, in contrast to 17 out of 29 patients without hyposalivation (58.6%) who complained of xerostomia. Altered saliva composition rather than the quantity of saliva may play a role in the induction of xerostomia.[8] Hyposalivation in DM patients can result in complications that affect the oral mucous membrane, such as dryness, sores, atrophy, mucositis, ulcers, opportunistic infections (fungi, bacteria, viruses), decreased papillation of the tongue, and increased risk of dental caries.[30] In the presentstudy, a direct relationship was observed between the patients who stated having a low amount of saliva (n=5) and those who had difficulty in swallowing food (n= 3) (Table I).

The number of patients who stated they had a “dry mouth” was higher than the number of those with hyposalivation because xerostomia may occur in spite of the presence of a normal saliva flow rate.[7] If Tables I and II are analyzed simultaneously they show that 8 out of the 12 patients “needing to drink,” 3 out of the 5 with “low amount of saliva,” and all 3 patients with “difficulty in swallowing” had stated having a “dry mouth.” The need to drink liquids during meals was reported by 12 adolescents with DM1 (23.5%). Similar data to these results was found in elderly DM1 patients (21.2%).[31] Although there was no significant difference between subjects with and without xerostomia, when “need to drink” was evaluated as an independent variable (p = .225; Table II), subjects with xerostomia (n= 8) showed more necessity to have something to drink to be able to swallow food compared with subjects without xerostomia (n= 4) (OR 2.11, 95% confidence interval 0.059-0.235; Table II). Nevertheless, in spite of this relationship between xerostomia and “need to drink,” it should be emphasized that familiar 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 to be able to swallow food. The clinical importance of the need to drink during meals among adolescents with DM1 and xerostomia needs to be further investigated in other studies.

The number of years the patients had been diagnosed as having the DM1 diagnosis and metabolic control levels were considered for their importance in relation to impact of xerostomia on QOL. In the present study, neither "time with DM1" (≤ 9 years or > 9 years) nor metabolic control levels (CG and HbG levels indicating well or poorly controlled) differed between the subjects with and without xerostomia ($P > .05$; Table II). There is not a consensus in the literature regarding the relationship between metabolic control and xerostomia and/or salivary function. Some studies assumed that levels of glycemic control were important for xerostomia and/or salivary function,[5,27,29,32,33] whereas others did not show this relationship.[28,34] The present study is in accordance with the latter.

In this study, when the impact of xerostomia on QOL was evaluated, OHIP-14 scores were higher in subjects with xerostomia (OHIP-14 score 7, negative impact) compared with subjects without xerostomia (OHIP-14 score 2.71, low impact) ($P < .001$; Table II). Xerostomia was shown to have a negative impact on the QOL of DM1 patients through the OHIP-14 evaluation. The same has been shown by other studies,[13,18,21,23] even when using other questionnaires to evaluate the impact of xerostomia on QOL,[16] or when comparison was made between OHIP-14 and another questionnaire.[12,14,15]

In the present study, the average OHIP-14 score was 5.2, varying between 0 and 16 points (Table I). A similar average score was found among elderly people (OHIP-14 score 5.6, varying between 0 and 48 points).[23] Meanwhile, Gerdin et al.[21] observed an average OHIP-14 score of 3, varying between 0 and 26, when evaluating the impact of xerostomia on the QOL of institutionalized elderly people. Ikebe et al.,[13] however, described an average OHIP-14 score of 11.5 points, showing elevated negative impact values for xerostomia and hyposalivation on the QOL of elderly people. The average OHIP-14 scores as well the variation intervals present great variations among the studies, but they concur that xerostomia causes negative impact on all of the OHIP-14[18] dimensions. The presence of other systemic conditions, except for DM, and the chronic use of multiple drugs that could influence oral health in elderly people should be taken into account when interpreting OHIP-14 scores.

Adolescents with DM1 valued social involvement with friends,[3] and the negative impact of xerostomia on QOL could be seen to hinder this social involvement. In the present study, the number of replies indicating negative impact to the questions involving both social incapacity and social disadvantages was significantly higher than the number of replies not

indicating impact in subjects with xerostomia ($P < .01$; Table III). Therefore, addressing and preventing xerostomia could improve adherence to DM1 treatment and monitoring as well as combating its consequences on the daily lives of adolescents with DM1.

Xerostomia was shown in this study to have a negative impact on QOL of adolescents with DM1. However, the findings in this cross-sectional study make direct comparisons with other studies in adults difficult. Multicenter follow-up studies with an increased subject number, control groups, and clinical measures repeated over multiple visits should be performed to evaluate the progression of DM1 in adolescents and the impact of xerostomia on QOL of these subjects.

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TABLES

Table I. Characteristics of the studied population.

Variables	n	% or average	(min-max)	SD
Age	51	17.2	(14-19)	1.36
Sex	51			
Female	27		52.9	
Male	24		47.1	
Time with DM1	51			
Up to 9 years	30		58.8	
Over 10 years	21		41.2	
CG	50	200.46	(47-463)	108.09
≤ 89 mg/dL	7		14.0	
90 -130 mg/dL	10		20.0	
≥ 131 mg/dL	33		66.0	
HbG	47	9.8	(5.7-15.3)	2.36
≤ 8.0%	13		27.7	
> 8.0%	34		72.3	
OHIP-14	51	5.2	(0-16)	4.58
0	4		7.8	
1 - 3	20		39.3	
4 - 6	10		19.6	
7 - 10	10		19.6	

11 - 16	7		13.7	
Xerostomia	51			
Yes	27		52.9	
No	24		47.1	
Amount of saliva referred	51			
Low	5		9.8	
Normal	46		90.2	
Difficulty in swallowing	51			
Yes	3		5.9	
No	48		94.1	
Need to drink	51			
Yes	12		23.5	
No	39		76.5	
SSFR	49	0.917	(0.196-2.953)	0.540
Hyposalivation	49			
Yes (SSFR ≤ 0.7 mL/min)	20		40.8	
No (SSFR > 0.7 mL/min)	29		59.2	

HbG - Glycosylated Hemoglobin
CG - Capillary Glucose
SSFR – Stimulated Salivary Flow Rate
OHIP-14 - Oral Health Impact Profile

Table II. Analysis of xerostomia as a dependent variable showing the independent variables in terms of average (± SD) or number of occurrences, odds ratio, and p value.

		Dependent variable: Xerostomia				
Independent Variables		**Yes**	**No**	**n**	**OR†**	**p value**
Age	average (± SD)	17.48 (±1.25)	16.92 (±1.44)	NA	NA	0.167[a]
Sex	Female	13	14	27	0.66	0.328[b]
	Male	14	10	24		
Time with DM1	≤ 9 years	8	8	16	1.04	0.586[b]
	> 9 years	10	7	17		
OHIP-14	average (± SD)	7 (± 5)	2.71 (± 2)	NA	NA	0.000[c]*
CG	Well-controlled	5	5	10	0.82	0.526[b]
	Poorly-controlled	22	18	40		
HbG	HbG <8.0%	7	6	13	1.04	0.608[b]
	HbG >8.1%	18	16	34		
SSFR	average (± SD)	0.944(±0.573)	0.885(±0.508)	NA	NA	0.563[a]
Hyposalivation	SSFR < 0.7	10	10	20	0.71	0.380[b]
	SSFR ≥ 0.7	17	12	29		
Need to drink	Yes	8	4	12	2.11	0.225[b]
	No	19	20	39		
Amount of saliva referred	Low Normal	3 24	2 22	5 46	1.38	0.557[b]
Difficulty in swallowing	Yes No	3 24	0 24	3 48	0.00	0.140[b]

NA – not applicable
OHIP-14 - Oral Health Impact Profile
SSFR – Stimulated Salivary Flow Rate (mL/min)
a Student t test
b Fisher's exact test
c Mann-Whitney Test
* $p \leq 0.05$
† CI 95 % around weighted probability

Table III. Number of replies with negative impact (sometimes, frequently and always) and without impact (rarely and never) per question and OHIP-14 dimensions compared with the presence of xerostomia.

Variables	Xerostomia	
Dimension	**n**	**p value [a]**
Functional limitation		
1- Have you had trouble pronouncing any word because of problems with your mouth?		
Negative impact	20	0.019*
Without impact	7	
2- Have you felt that your sense of taste has worsened because of problems with your mouth?		
Negative impact	9	0.009†
Without impact	18	
Physical pain		
3- Have you had painful aching in your mouth?		
Negative impact	20	0.038*
Without impact	7	
4- Have you found it uncomfortable to eat any foods because of problems with your mouth?		
Negative impact	11	0.285
Without impact	16	
Psychological discomfort		
5- Have you been self-conscious because of problems with your mouth?		
Negative impact	13	0.078
Without impact	14	
6- Have you felt tense because of problems with your mouth?		
Negative impact	20	0.002†
Without impact	7	
Physical incapacity		
7- Has your diet been unsatisfactory because of problems with your mouth?		
Negative impact	12	0.013*
Without impact	15	
8-. Have you had to interrupt meals because of problems with your mouth?		
Negative impact	9	0.009†
Without impact	18	
Psychological incapacity		
9- Have you found it difficult to relax because of problems with your mouth?		
Negative impact	17	0.001†

Without impact	10	
10- Have you been a bit embarrassed because of problems with your mouth?		
Negative impact	14	0.022*
Without impact	13	
Social incapacity		
11- Have you been a bit irritable with other people because of problems with your mouth?		
Negative impact	21	0.009†
Without impact	6	
12- Have you had difficult doing your usual jobs because of problems with your mouth?		
Negative impact	18	0.001†
Without impact	9	
Social disadvantage		
13- Have you felt that life in general was less satisfying because of problems with your mouth?		
Negative impact	16	0.002†
Without impact	11	
14- Have you been totally unable to function because of problems with your mouth?		
Negative impact	10	0.005†
Without impact	17	

[a] Fisher's Exact Test

* $p \leq 0.05$

† $p \leq 0.01$

5.ARTIGO 2

Association between metabolic control and oral health in adolescents with type 1 diabetes mellitus

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ABSTRACT

Objectives: To evaluate the association between metabolic control and oral health of adolescents with type 1 diabetes mellitus (DM1).

Study design: A case-control epidemiologic study was performed on adolescents allocated between two groups: DM1-group comprised of 51 with DM1; control group, comprised of 51 non-diabetics. In DM1-group, metabolic control data were observed (glycosylated hemoglobin – GHb, capillary glucose), whereby GHb ≤ 8.0% was considered to indicate good metabolic control (DM1-A) and > 8.0%, poor metabolic control (DM1-B). Clinical examination was performed to evaluate the presence of oral manifestations, Community Periodontal (CPI) and DMF indices. Salivary flow was evaluated by means of stimulated saliva collection (SSFR).

Results: GHb values of ≤ 8.0% (DM1-A) were observed in 17 (24%) and > 8.0% (DM1-B) in 34 (76%) subjects. The average DMF index was 1.5 (control) and 3.3 (DM1-group) ($p \leq 0.05$). The average CP index was: 0.2 (control), 1.4 (DM1-A), 2.0 (DM1-B) ($p \leq 0.05$). Average SSFR was 0.903 mL/min (DM1-B) and 1.224 mL/min (control) ($p=0.003$).

Conclusions: The oral health of adolescents with DM1 was impaired regardless of metabolic control.

KEY WORDS: type 1 diabetes mellitus; DMF index; flow rate; periodontal disease.

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Title: Association between metabolic control and oral health in adolescents with type 1 diabetes mellitus.
Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

Dear Dr. Busato,

I am writing concerning your paper, "Association between metabolic control and oral health in adolescents with type 1 diabetes mellitus.", which you recently submitted to Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. Your paper has once again been carefully reviewed. I am pleased to inform you that your revised paper has been revised by the Editor and accepted for publication in the electronic version of the Journal.

On-line only articles in Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology are fully indexed for the MEDLINE database maintained by the National Library of Medicine and abstracts arefreely accessible via the PubMed online platform. On-line only articles are also indexed by Thomson Scientific for their Web of Science database.

Edited galley sheets will be e-mailed to you in the reasonably near future.

Thank you for preparing this informative article for the readership of the Journal. I hope you will also consider us again in the future.

Sincerely yours,

Craig Miller, DMD, MS
Section Editor, Oral Medicine
Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology

INTRODUCTION

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.[1] The American Diabetes Association (ADA) reports that 75% of DM1 cases are diagnosed in persons under the age 18 years.[2]

Maintaining metabolic control of DM1 in adolescents is a significant challenge for health professionals.[3] Glycemic control has a modifying effect on the relation between dental caries and salivary factors in young patients.[4] Salivary hypofunction in diabetic patients may be a response to inadequate metabolic control of the diabetes.[5,6]

The influence of DM1 on oral health has been widely studied,[7-24]but few studies investigated adolescents with DM1.[13,18-20,24]Among them, two studies[13,20] evaluated only the periodontal changes with DM1 and one[19] described the presence of dental caries in children and adolescents with DM1. DM1 has increased dental caries experience[5,18] as well as predisposition to periodontal disease.[5,25] Stimulated salivary flow reduction has been observed in DM1 patients and is considered to be a risk factor for dental caries.[25] Furthermore, dry mouth (xerostomia) was shown to have a negative impact on the quality of life of adolescents with DM1.[24]

There has been an increased prevalence of dental caries in young DM1 adults with poor metabolic control[8] and diabetic adults.[16] Metabolic control and traditional caries risk markers are important factors for caries development in children and adolescents with DM1.[9] Due to the presence of few studies directed to investigate the oral health of both well and poorly controlled adolescents with DM1, the aim of this study was to evaluate the association between metabolic control and oral health (presence of oral mucosa lesions, caries experience, periodontal conditions, salivary flow rate) in these patients.

MATERIAL 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.

Study group and study design

A case-control epidemiologic study was performed on adolescents aged 14 to 19 years, allocated between two groups: DM1-group comprised of 51 adolescents with DM1, who receive follow-up at the Diabetes Outpatients Department of the Paraná Federal University Teaching Hospital, and control group comprised of 51 non-diabetic subjects who were recruited from public high schools. DM1-group and control group were paired regarding gender and age. DM1 diagnosis using the ADA[1] 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 or illicit drugs users and alcohol users.[24]

Evaluation of metabolic control

The results of glycosylated hemoglobin (GHb) tests performed less than three months prior to saliva collection and the results of capillary glucose (CG) tests performed at the time of saliva collection were collected from the medical records. The GHb tests were performed in the Laboratory of Chemical Analysis at the Paraná Federal University Teaching Hospital. The CG tests were performed by nurses at the Diabetes Outpatients Department of the Paraná Federal University Teaching Hospital. Patients with good metabolic control were considered to be those with GHb values of ≤ 8.0 % (DM1-A group), whereas poorly-controlled patients were considered to be those with GHb values of > 8.0 % (DM1-B group). CG values between 90 and 130 mg/dL characterized good glycemic control.[2]

Clinical examinations

Oral health assessment was performed by an appraiser and consisted of three examinations: physical intraoral examination, periodontal evaluation and dental caries experience. Any alteration to oral mucosa was recorded. The Community Periodontal Index – CPI was used for periodontal evaluation. The examination was performed using a WHO-probe. The mouth was divided into sextants using the first molar in each quadrant, right upper central, and left mandibular central. The CPI was coded as: 0=healthy, 1=bleeding, 2=calculus, 3=periodontal pocket between 4/5 mm, 4=periodontal pocket > 6mm.[27] The CPI was evaluated by summing the values of the six index teeth, whereby the total could vary between 0 and 24. Dental caries experience was observed using the DMF

index (decayed, missing, filled). The examination was performed using a flat clinical mirror to check the teeth for DMF. The diagnosis criteria followed those proposed by WHO.[27]

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 salivary flow rate (SSFR) was evaluated by means of the gravimetric method and expressed in mL/min[28]. SSFR values of > 0.7 mL/min were considered to represent normal salivary flow.[29]

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. Other tests used were the Mann-Whitney test, Chi-square test and Fisher's Exact test, considering statistically significant values ($p \leq 0.05$ and IC 95%).

RESULTS

A total of 102 subjects were included in the study. Fifty-one patients had DM1 (DM1-group) and 51 did not have DM1 (control group). Twenty-seven individuals were female (52.9%) and 24 were male (47.1%) in each group (DM1-group and control). Average age was 17 years (range 14-19, SD 1.4). GHb values of ≤ 8.0% (DM1-A) were observed in 17 subjects (24%) and GHb > 8.0% (DM1-B) in 34 subjects (76%). Average GHb was: 9.8% (DM1-group), 7.2% (DM1-A), and 10.6% (DM1-B). The average CG in DM1-group was 200.5 mg/dL, whilst in DM1-A and DM1-B it was 177.2 mg/dL and 207.6 mg/dL, respectively. The average time since DM1 diagnosis was 8.5 years in DM1-group, 6.9 years in DM1-A and 9.4 years in DM1-B (Table 1).

The prevalence of oral mucosa manifestations was low both in DM1-group, 21.6% (n = 11), and in control group, 3.9% (n = 2), with statistical difference between groups (p = 0.007). Oral manifestations in DM1 adolescents were more prevalent in DM1-B (n = 9)

than in DM1-A (n = 2) groups (Table 2). The most frequent manifestation diagnosed was fissured tongue for both DM1 adolescent groups, DM1-B (10.5%, n = 4) and DM1-A (7.7%, n = 1). In control group, it was noteworthy that 49 adolescents (96.2%) had no oral manifestation (healthy) compared with 11 adolescents (84.8%) in DM1-A and 29 (76.3%) in DM1-B. There was statistical difference between control group and DM1-B group for the presence of healthy mucosa (p = 0.029) (Table 3).

The average CPI was 1.8 in DM1-group and 0.2 in control group (p = 0.000). Adolescents with poor metabolic control presented a CPI of 2.0 (DM1-B) whilst this index was 1.4 in the group with good metabolic control (DM1-A). There was statistical difference between DM1-A and controls, and between DM1-B and controls in relation to the CPI ($p \leq 0.05$) (Table 2). The periodontal evaluation revealed average healthy teeth indices in DM1-A, DM1-B and controls of 5.4, 5.1 and 5.9, respectively. There was statistical difference between DM1-A and control group; and between DM1-B and control group for the presence of periodontally healthy teeth (p = 0.000). Periodontal pockets were not found in any of the groups. Average teeth indices of bleeding after probing were 0.6 (DM1-A) and 0.7 (DM1-B), with statistical difference between DM1-A and controls (0.0), and between DM1-B and controls (0.0), p = 0.000 (Table 3).

The DMF index in DM1-group was 3.3 whilst in control group it was 1.5 (p = 0.020) (Table 2). The DMF index in DM1-A and in DM1-B was 3.6 and 3.2, respectively. There was statistical difference between DM1-A and controls (p = 0.050). The healthy teeth average with regard to caries among the adolescents was 23.7 (DM1-A), 24.6 (DM1-B) and 26.3 (controls), with statistical difference between DM1-A and controls (p = 0.041). On average DM1-A had 0.5 decayed teeth, DM1-B had 0.3, and controls had 0.2, without statistical difference between the groups. None of the adolescents in the control group had lost any teeth because of caries, whilst in the groups of adolescents with DM1, average tooth loss was 0.5 (DM1-A) and 0.1 (DM1-B). There was statistical difference between DM1-A and controls (p = 0.005), and between DM1-B and controls (p = 0.042) for the number of missing teeth. The following averages were found for restored teeth among the groups of adolescents: DM1-A (3.3), DM1-B (2.9) and controls (1.5), with no statistical differences between groups (Table 3).

Average SSFR was 0.932 mL/min in DM1-group and 1.224 mL/min in control group, with statistical difference between groups (p=0.003) (Table 2). SSFR in the group with poor

metabolic control (DM1-B) was 0.903 mL/min whilst in the group with good metabolic control (DM1-A) it was 0.997 mL/min. There was statistical difference between DM1-B and controls for SSFR (p=0.003) (Table 2).

DISCUSSION

In the present study, poor metabolic control (GHb > 8.0%) prevalence in DM1 adolescents was 76%, demonstrating that maintaining metabolic control during adolescence is complex.[3] DM1 and poor metabolic control in adolescents seemed to reduce stimulated salivary flow, and to increase both the presence of lesions in the oral mucosa and periodontal disease. DM1 in adolescents, regardless of metabolic control, increased caries experience. The results of this study confirmed that oral health (presence of oral mucosa lesions, caries experience, periodontal disease, salivary flow rate) was impaired in adolescents with DM1, whilst reinforcing the need to monitor the oral health of these patients.

The prevalence of oral mucosa manifestations is low during adolescence.[13] Oral mucosa manifestations were present in 21.6% (n = 11) of the DM1 adolescents, with this prevalence being concentrated in the group with poor metabolic control (DM1-B, n = 9) (Table 2). Despite the greater prevalence of oral manifestations was concentrated in the DM1 adolescent group with poor metabolic control, their prevalence was low. Fissured tongue was the most frequent oral manifestation (n = 4, 10.5%). In this study the prevalence of fissured tongue in poorly-controlled adolescents with DM1 was higher than fissured tongue prevalence in DM1 adults among whom prevalence was 5.4%[15] and in DM2 adults who had 6.7% prevalence.[30]

In the present study, the CPI was 1.8 in DM1 adolescents while in adolescents and young adults with DM1,[11] this value was 1.65. Both the poorly-controlled (GHb > 8.0%, DM1-B) and the well-controlled (GHb ≤ 8.0 %, DM1-A) patients showed CPI values different from the controls, emphasizing that regardless of the metabolic control, the CPI values were higher in adolescents with DM1. The association between periodontal disease and metabolic control has been indicated in some studies.[11,17,25] Studies with DM1 children and adolescents[7,11-13,20] confirmed that periodontal disease is an important oral health problem.

Bleeding following probing was the most frequent periodontal problem observed in the DM1 adolescents (DM1-A and DM1-B groups), highlighting the importance of

prevention and monitoring of DM1 adolescents by oral health professionals to avoid the progression of the disease and resulting impairment of the overall health of these patients. Periodontal control of DM1 should be established very early, even in the presence of good metabolic control of the disease.[11] Glycemic control is a consistent risk factor associated with the extent and severity of periodontal disease.[17] The evidence reviewed supports diabetes having an adverse effect on periodontal health and periodontal infection having an adverse effect on glycemic control.[25] The treatment of periodontal infection is important for maintaining and stabilizing glycemic control and makes possible the reduction of diabetes-related complications.[25]

Analysis of the DMF index in DM1 adolescents has indicated that the prevalence of dental caries experience was low (3.3) compared with studies with DM1 children (DMF = 9.64)[19] and DM1 adolescents (DMF = 5.66)[14], or studies with young DM1 adults (DMF = 10.1[8] and DMF = 6.7[21]). In this study metabolic control did not show itself to be an important factor for dental caries, and this result was also found in other studies with DM1 children and adolescents.[6,18,22] Conversely, there was association between poor metabolic control and dental caries in the literature.[4,8-10,16,23] The sample size may have interfered in the results, making it difficult to indicate an association between poor metabolic control and dental caries experience.

The average SSFR value was statistically different between DM1-group (0.932 mL/min) and control group (1.224 mL/min) and this agrees with previous studies with DM1 children[6] and DM1 adolescents.[12] Aren et al[7] did not find statistical difference between average SSFR (0.86 mL/min) in DM1 adolescents compared to adolescents without DM1. In the present study, poor metabolic control contributed to the reduction in salivary flow (Table 2), in contrast to studies with DM1 children[6] and young DM1 adults,[8] which did not find this relationship. Low salivary flow can influence increased caries experience in DM patients.[6,26] Moreover, 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.[24]

The oral health of DM1 adolescents was impaired regardless of metabolic control. Including the dentist in the multiprofessional accompaniment of DM1 adolescents should help to prevent the worsening of their oral health problems, thus contributing towards maintaining and stabilizing glycemic control.

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TABLES

Table 1. Characteristics of the studied population.

Variables			DM1-group	DM1-A GHb ≤ 8.0%	DM1-B GHb > 8.0%	Control group
			N = 51	N = 17	N = 34	N = 51
Age (years)		mean (SD)	17.2 (1.4)	17.1 (1.2)	17.2 (1.4)	17.0 (1.4)
Gender	female	n (%)	27 (52.9)	10 (58.8)	17 (50.0)	27 (52.9)
	male	n (%)	24 (47.1))	7 (41.2)	17 (50.0)	24 (47.1)
Time with DM1 (years)		mean (SD)	8.5 (4.9)	6.9 (5.1)	9.4 (4.7)	-
CG (mg/dL)		mean (SD)	200.5 (108.1)	177.2 (103.2)	207.6 (108.4)	-
GHb (%)		mean (SD)	9.8 (2.4)	7.2 (0.8)	10.6 (1.9)	-

DM1: type 1 diabetes mellitus
DM1-group: adolescents with DM1, DM1-A: adolescents with DM1 with good metabolic control,
DM1-B: adolescents with DM1 with poor metabolic control, Control group: adolescents without DM1
GHb - Glycosylated hemoglobin, CG - capillary glucose

Table 2. Analysis of diabetes mellitus as a dependent variable showing the independent variables.

Variables		DM1-group	DM1-A GHb ≤ 8%	DM1-B GHb > 8%	Control Group	P value
		N = 51	N = 17	N = 34	N = 51	
Mucosa lesions	n (%)	11 (21.6)	2 (16.7)	9 (23.1)	2 (3.9)	0.007 [a Ŧ] NS [b,c]
CPI	mean (SD)	1.8 (1.8)	1.4 (1.4)	2.0 (2.0)	0.2 (0.8)	0.000 [a*]
	median [range]	1.0 [0-7]	1.0 [0-4]	1.5 [0-7]	0.0 [0-5]	0.000 [b*] 0.000 [c*]
DMF index	mean (SD)	3.3 (3.7)	3.6 (3.7)	3.2 (3.7)	1.5 (2.1)	0.020 [a*]
	median [range]	2.5 [0-13]	3.0 [0-11]	2.0 [0-13]	1.0 [0-10]	0.050 [b*] NS [c]
SSFR (mL/min)	mean (SD)	0.932 (0.537)	0.997(0.442)	0.903 (0.577)	1.224 (0.577)	0.003 [a*]
	median [range]	0.862 [0.196-2.953]	0.942 [0.486-2.334]	0.793 [0.196-2.953]	1.128 [0.420-3.125]	NS [b] 0.003 [c*]

DM1-group: adolescents with DM1, DM1-A: adolescents with DM1 with good metabolic control, DM1-B: adolescents with DM1 with poor metabolic control, Control group: adolescents without DM1
SSFR: stimulated salivary flow rate, DMF índex: Decayed, Missing and Filled, CPI: Community Periodontal Index
[a] p value of DM1-group X control group
[b] p value of DM1-A X control group
[c] p value of DM1-B X control group
* Mann-Whitney U test, ŦChi-square test, NS no-significant (p > 0.05)

Table 3. Characteristics of the oral health of adolescents.

Oral health		DM1-A GHb ≤ 8% N = 17	DM1-B GHb > 8% N = 34	Control Group N = 51	P value
Mucosa lesions					
Healthy	n (%)	11 (84.6)	29 (76.3)	49 (96.2)	NS[a] 0.029[b∓] NS[c]
Fissured tongue	n (%)	1 (7.7)	4 (10.5)	1 (1.9)	NS[a,b,c]
Traumatic ulcer	n (%)	0 (0.0)	2 (5.3)	1 (1.9)	NS[a,b,c]
Angular cheilitis	n (%)	1 (7.7)	2 (5.3)	0 (0.0)	NS[a,,b,c]
Candidiasis (palate)	n (%)	0 (0.0)	1 (2.6)	0 (0.0)	NS[a,b,c]
Periodontium					
Healthy	mean (SD)	5.4 (0.5)	5.1 (0.6)	5.9 (0.4)	0.000[a*] 0.000[b*] NS[c]
Bleeding gingival	mean (SD)	0.6 (0.5)	0.7 (0.4)	0.0 (0.0)	0.000[a*] 0.000[b*] NS[c]
Calculus	mean (SD)	0.0 (0.0)	0.2 (0.4)	0.1 (0.2)	NS[a,b,c]
Teeth					
Healthy	mean (SD)	23.7 (4.1)	24.6 (4.0)	26.3 (2.2)	0.041[a*] NS[b,c]
Decayed	mean (SD)	0.5 (1.2)	0.3 (1.0)	0.2 (0.5)	NS[a,b,c]
Missing	mean (SD)	0.5 (1.1)	0.1 (0.5)	0.0 (0.0)	0.005[a*] 0.042[b*] NS[c]
Filled	mean (SD)	3.3 (4.0)	2.9 (3.5)	1.5 (2.6)	NS[a,b,c]

DM1-A: adolescents with DM1 with good metabolic control, DM1-B: adolescents with DM1 with poor metabolic control, Control group: adolescents without DM1

[a] p value of DM1-A X control group

[b] p value of DM1-B X control group

[c] p value of DM1-A X DM1-B

∓ Chi-square test, * Mann-Whitney U test, NS no-significant ($p > 0.05$)

6.ARTIGO 3

Impacto da hiperglicemia na composição e fluxo salivar e na xerostomia de adolescentes com *diabetes mellitus* tipo 1

Artigo segue as normas da Revista *Oral Diseases* disponível no site: http://www.wiley.com/bw/journal.asp?ref=1354-523x

Resumo

Objetivo: Avaliar a associação entre hiperglicemia, fluxo e composição salivar, e xerostomia em adolescentes com *diabetes mellitus* tipo 1 (DM1).

Materiais e Métodos: Estudo epidemiológico caso-controle com adolescentes alocados em dois grupos: grupo DM1, composto por 51 adolescentes com DM1; grupo controle, composto por 51 adolescentes sem DM1. No grupo DM1, foram observados dados de glicose capilar (GC). Adolescentes com bom controle glicêmico foram considerados aqueles com valores de CG ≤ 130 mg/dL (grupo DM1-A). A hiperglicemia foi considerada para adolescentes com valores de CG > 130 mg/dL (grupo DM1-B). Xerostomia foi detectada com perguntas sobre a sensação de "boca seca". Fluxo salivar foi avaliado por meio da coleta de saliva estimulada (FSE). Concentrações salivares de proteínas totais, amilase, ureia, cálcio e glicose foram obtidas.

Resultados: Um total de 65% (n=33) dos adolescentes do grupo DM1 apresentou hiperglicemia. A presença de xerostomia foi indicada por 27 (53%) adolescentes no grupo DM1 e 8 (16%) no grupo controle ($P < 0,001$). Os valores médios de FSE foram 0,932 mL/min no grupo DM1, 1,224 mL/min no grupo controle e 0,812 mL/min no DM1-B, com diferença significante entre grupos DM1 e controle, e DM1-B e controle ($P < 0,05$). Análise da composição bioquímica da saliva mostrou diferença significante entre DM1-B e grupo controle para ureia ($P = 0,042$), cálcio ($P < 0,001$) e glicose ($P = 0,038$).

Conclusão: A hiperglicemia foi fator de risco para redução de FSE e aumento da concentração salivar de ureia e cálcio.

Palavras-chaves: *diabetes mellitus* tipo 1, fluxo salivar, adolescentes, composição salivar, xerostomia, hiperglicemia.

Introdução

O *diabetes mellitus* tipo 1 (DM1) é uma disfunção metabólica caracterizada pela hiperglicemia resultante da deficiência definitiva na secreção de insulina, provocada por doença auto-imune e fatores genéticos (ADA, 2004). *American Diabetes Association* (ADA) afirma que 75% dos casos de DM1 são diagnosticados em pessoas abaixo de 18 anos (ADA, 2006). O controle glicêmico é fundamental para o acompanhamento do diabetes, e está associado com a diminuição da freqüência de complicações microvasculares (retinopatia e nefropatia) e neuropáticas (ADA, 2008). O controle glicêmico pode apresentar efeito modificador na relação entre cárie dental e fatores salivares em pacientes jovens (Syjälä *et al* 2003).

A sensação subjetiva de boca seca (xerostomia) é uma das manifestações bucais do diabetes (Sreebny *et al* 2006; von Bültzingslöwen *et al* 2007). Xerostomia pode resultar da redução da secreção salivar ou ocorrer na presença de fluxo salivar normal (Guggenheimer e Moore 2003; Scully 2003). Tanto alterações na composição da saliva como na quantidade de saliva podem induzir a xerostomia (Anttila *et al* 1998; Fox 1996).

Pacientes com DM1, particularmente aqueles com mau controle glicêmico, podem apresentar diminuição do fluxo salivar (Guggenheimer e Moore 2003). Muitos problemas clínicos podem se desenvolver na presença de xerostomia, tais como: dificuldade de deglutir e falar, alta suscetibilidade a infecções bucais (principalmente candidose e cárie dental), gengivite e mucosite (Anttila *et al* 1998). Além disso, a xerostomia mostrou ter impacto negativo na qualidade de vida de adolescentes com DM1 (Busato *et al* 2009).

A relação entre DM1, composição e fluxo salivar, e xerostomia tem sido amplamente investigada (Swanljung *et al* 1992; Moore *et al* 2001; López *et al* 2003; Siudikiene *et al* 2006; Siudikiene *et al* 2008; Orbak *et al* 2008; Sreebny *et al* 2006; von Bültzingslöwen *et al* 2007). Foi observado que a maioria dos pacientes com DM1 apresenta disfunção salivar assim como alterações na composição bioquímica da saliva quando comparada a indivíduos saudáveis (Swanljung *et al* 1992; Moore *et al* 2001; López *et al* 2003; Siudikiene *et al* 2006; Siudikiene *et al* 2008; Orbak *et al* 2008). No entanto, há escassez de trabalhos que mostrem a relação da hiperglicemia com alterações na quanlidade e na quantidade de saliva e com a xerostomia, especialmente em adolescentes com DM1. Assim, o objetivo deste estudo foi avaliar a associação entre hiperglicemia, xerostomia, composição e fluxo salivar em adolescentes com DM1.

Materiais e Métodos

O presente estudo foi aprovado pelo Comitê de Ética em Pesquisa da PUCPR e pela Direção do Hospital de Clínicas do Paraná - UFPR. Pacientes e responsáveis foram informados sobre o objetivo e demais aspectos da pesquisa e assinaram o Termo de Consentimento Livre e Esclarecido.

Grupos do estudo e design do estudo

Estudo epidemiológico de caso-controle consistiu de adolescentes alocados em dois grupos: grupo controle, composto por 51 não-diabéticos, recrutados em escolas públicas de ensino médio; e grupo DM1, composto por 51 adolescentes com DM1, acompanhados no Ambulatório de Diabetes do Hospital de Clínicas - Universidade Federal do Paraná. Grupos DM1 e controle foram pareados em sexo e idade (14-19 anos). A classificação da ADA (2006) foi usada para diagnóstico de DM1 e estabelecida como critério de inclusão do grupo DM1. O critério de inclusão para o grupo controle foi de adolescentes não-diabéticos que não fizeram uso de qualquer fármaco há menos de um mês. Os critérios de exclusão para ambos os grupos (DM1 e controle) foram: presença de condições sistêmicas que pudessem influenciar a fisiologia das glândulas salivares, indivíduos fumantes, etilistas ou usuários de drogas ilícitas ou psicotrópicas (Busato *et al* 2009).

Controle glicêmico

Os resultados dos testes de glicose capilar (GC) pós-prandial, realizados no momento da coleta da saliva, foram registrados. Pacientes com bom controle glicêmico foram considerados aqueles que apresentaram valores de CG ≤ 130 mg/dL (grupo DM1-A). A hiperglicemia foi considerada para pacientes com valores de CG > 130 mg/dL (grupo DM1-B) (ADA, 2006; 2008).

Xerostomia

Xerostomia foi definida como sensação de boca seca relatada pelo paciente. A xerostomia foi detectada pela pergunta: você tem tido sensação de “boca seca” diariamente nos últimos seis meses? (questão A). Respostas “sim” foram consideradas como presença de xerostomia 1. Essa avaliação foi completada pelas perguntas: como você descreve a quantidade de saliva na sua boca? (questão B); você tem dificuldade para engolir a comida? (questão C); e, você precisa de uma bebida para engolir as refeições? (questão D). (Carda *et al* 2006).

Xerostomia foi categorizada em três escalas de percepção: xerostomia 1 (boca seca), quando houve resposta "sim" para questão A; xerostomia 2 foi considerada presente quando houve resposta positiva para a questão A e para uma das questões (B, C ou D); xerostomia 3, foi considerada presente quando houve resposta positiva para a questão A e para mais duas questões relacionadas a xerostomia (B, C ou D).

Coleta e tratamento da saliva

A saliva foi coletada com a utilização de estímulo mastigatório mecânico, por meio de pedaço de látex para garrote estéril de tamanho padronizado (1,5 cm), mastigado continuamente pelo paciente durante 6 minutos. A saliva produzida durante o primeiro minuto de estimulação foi desprezada. Durante os 5 minutos subseqüentes, o paciente expeliu a saliva no interior de um pote coletor universal esterilizado e previamente pesado, numa balança analítica - Marte®, modelo AL 500 (SP – Brasil). A saliva foi coletada no período entre 8:00 horas e 10:00 horas. O fluxo salivar estimulado (FSE) foi avaliado por meio do método gravimétrico, expresso em mL/min (Banderas-Tarabay *et al* 1997).

Antes de submeter as amostras de saliva às provas bioquímicas, estas foram centrifugadas (3.000 g por 10 min). Concentrações salivares de proteínas totais e cálcio foram determinadas pelo método colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de amilase foi determinada pelo método cinético colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de ureia foi determinada pelo método enzimático colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de glicose foi determinada pelo método enzimático colorimétrico (Kits BIOCLIN®/Belo Horizonte - MG/ Brasil). Os testes bioquímicos salivares foram realizados em triplicata.

Análise estatística

A análise dos dados foi realizada usando o *SPSS versão 15.0 for Windows*. Análise de normalidade usada foi o Teste de Kolmogorov-Smirnov e o teste de Levene avaliou a homogeneidade de variância. Foram usados testes de Mann-Whitney e Exato de Fisher's, considerando valores estatisticamente significantes ($p \leq 0,05$ e IC 95%).

Resultados

Um total de 102 adolescentes foi incluído neste estudo: 51 pacientes com DM1 (grupo DM1) e 51 adolescentes sem DM1 (grupo controle). Vinte e sete adolescentes foram do sexo feminino (52,9%) e 24, do sexo masculino (47,1%) em ambos os grupos (DM1 e

controle). A idade média foi de 17 anos (14-19, DP = 1,4) em ambos os grupos. No grupo DM1, a média de GC foi 200,5 mg/dL (DP = 108,09). Trinta e três (65%) adolescentes apresentaram hiperglicemia (grupo DM1-B), enquanto 18 (35%) apresentaram bom controle glicêmico (grupo DM1-A).

A presença de xerostomia 1 (boca seca) foi indicada por 27/51 (53%) adolescentes no grupo DM1 e 8/51 (16%) no grupo controle ($P < 0,001$) (Tabela 1). Entre adolescentes com bom controle glicêmico (DM1-A), 11/18 (61%) indivíduos apresentaram xerostomia 1, em contraste com 16/33 (48%) adolescentes com hiperglicemia (DM1-B). Houve diferença significante entre grupos DM1-A e controle, e DM1-B e controle para xerostomia 1 ($P < 0,05$) (Tabela 2). Um total de 12 adolescentes com DM1 (24%) apontou necessitar de líquidos durante as refeições no grupo DM1 em contraste com 2 (4%) adolescentes no grupo controle ($P = 0,004$). Os grupos DM1 e controle não mostraram diferença significativa para as questões: dificuldade para engolir e quantidade de saliva referida. Apenas adolescentes do grupo DM1 apresentaram xerostomia 2 (n=10, 10,2%) e xerostomia 3 (n=5, 5,1%). Houve diferença significante entre grupos (DM1 e controle) para xerostomia 2 ($P = 0,001$) e xerostomia 3 ($P = 0,028$) (Tabela 1).

A média de FSE foi de 0,932 mL/min no grupo DM1, e 1,224 mL/min no grupo controle ($P = 0,003$). No grupo com bom controle glicêmico (DM1-A), a média de FSE foi 1,140 mL/min, sem diferença significante comparado ao grupo controle ($p > 0,05$). No grupo de adolescentes com hiperglicemia (DM1-B), a média de FSE foi 0,812 mL/min e apresentou diferença significante quando comparada ao controle ($p = 0,002$) (Tabela 2).

Tabela 2 mostra as médias e desvios padrão das concentrações salivares de proteínas totais, amilase, ureia, cálcio e glicose nos grupos DM1, DM1-A, DM1-B e controle. Houve diferenças significativas entre grupos DM1 e controle para concentrações salivares de proteínas totais ($P = 0,009$), cálcio ($P = 0,001$) e glicose ($P = 0,021$). Quando o grupo DM1-A foi comparado ao controle, houve diferenças significativas para concentrações salivares de proteínas totais ($P = 0,007$) e glicose ($P = 0,024$). O grupo DM1-B (adolescentes com hiperglicemia) apresentou maiores concentrações salivares de ureia ($P = 0,042$), cálcio ($P < 0,001$) e glicose ($P = 0,038$) quando comparado ao grupo controle.

Discussão

No presente estudo, a hiperglicemia (GC > 130 mg/dL) esteve presente 33 (65%) adolescentes com DM1. O DM1, independente do controle glicêmico, foi fator de risco para presença de xerostomia e aumento de concentração salivar de glicose. A hiperglicemia foi fator de risco para redução do FSE e aumento da concentração salivar de ureia e cálcio.

A xerostomia 1 esteve presente em 27 (53%) adolescentes com DM1, sendo 11 no grupo DM1-A e 16, no DM1-B, em contraste com 8 (16%) adolescentes sem diabetes, que apresentaram xerostomia 1. A xerostomia foi significativamente associada com DM1 (Tabela 1) independente do controle glicêmico (Tabela 2). Xerostomia 2 e xerostomia 3 ocorreram apenas no grupo DM1, demonstrando que a xerostomia é uma manifestação bucal do diabetes (Sreebny *et al* 2006; von Bültzingslöwen *et al* 2007). A prevalência de xerostomia varia de 24,1% em idosos com DM1 (Moore *et al* 2001) a 76,4% em idosos com DM tipo 2 (Carda *et al* 2006). Contudo, são limitados os estudos na literatura que mostram a prevalência de xerostomia em adolescentes com DM1, dificultando a comparação deste estudo com outros estudos em adultos.

A necessidade de beber líquidos durante as refeições foi referida por 12 (24%) adolescentes com DM1 e por 2 (4%) adolescentes sem diabetes, com diferença significativa entre grupos (P = 0,004, Tabela 1). No entanto, apesar desta relação significativa entre DM1 e "necessidade de beber líquidos", deve ser enfatizado que hábitos familiares e individuais podem estar associados. O hábito de beber sucos, refrigerantes ou mesmo água durante as refeições é muito comum e frequentemente não indica uma necessidade real de beber líquidos para conseguir engolir a comida. A importância clínica desta necessidade de beber líquidos durante as refeições apontada por adolescentes com DM1 deve ser investigada em outros estudos.

No presente estudo, a média de FSE foi de 0,932 mL/min em adolescentes com DM1 e 0,812 mL/min em adolescentes com hiperglicemia. Ambas as médias citadas foram significativamente menores quando comparadas à média do FSE no grupo controle (1,224 mL/min) (P < 0,05). Valores médios de FSE variam de 0,79 mL/min em crianças e adolescentes com DM1 (Belazi *et al* 1998) a 1,17 mL/min em adolescentes com DM1 (Siudikiene *et al* 2006). O valor médio de FSE do trabalho de Siudikiene *et al* 2006 é similar ao valor médio do FSE de adolescentes com bom controle glicêmico (1,14 mL/min) obtido no presente estudo. Houve diferença significante para média de FSE entre grupos DM1 (0,932 mL/min) e controle (1,224 mL/min), em consonância com outros estudos com

adolescentes com DM1 (Siudikiene *et al* 2006; 2008). Neste estudo, a hiperglicemia foi associada com a redução do fluxo salivar (Tabela 2). Este resultado está em consonância com trabalho anterior, onde é sugerida que a desidratação associada à hiperglicemia pode contribuir para diminuição do volume de saliva excretada (Karjalainen *et al* 1996). O baixo fluxo salivar contribui para aumento da experiência de cárie em pacientes com DM (Siudikiene *et al* 2006, Márton *et al* 2008). Além disso, a sensação subjetiva de boca seca (xerostomia) pode resultar de uma redução na secreção salivar e mostrou ter impacto negativo na qualidade de vida de adolescentes com DM1 (Busato *et al* 2009).

A saliva contém proteínas imunológicas e não-imunológicas com propriedades antibacterianas (Humphrey e Williamson, 2001). Neste estudo, o bom controle glicêmico (grupo DM1-A) foi associado com a diminuição da concentração salivar de proteínas totais comparado aos não diabéticos. Por outro lado, não houve alterações significativas na concentração salivar de proteínas totais na presença de hiperglicemia (DM1-B) comparado ao grupo controle. Da mesma forma, as concentrações salivares de amilase nos adolescentes com DM1 não diferiram daquelas do grupo controle. Outros estudos (Twetman *et al*, 2002; Mata *et al,* 2004; Carda *et al* 2006; Moreira *et al*, 2009) mostraram diferenças significantes na concentração salivar de proteínas totais entre indivíduos com e sem DM1. Sugere-se investigar a influência da hipoglicemia na concentração salivar de proteínas totais em adolescentes com DM1.

A concentração de cálcio salivar é fundamental para a manutenção da integridade dos dentes e modulação da remineralização e desmineralização (Humphrey e Williamson, 2001). No presente estudo, a concentração salivar de cálcio no grupo DM1 foi significativamente maior comparada aquela do grupo controle, em consonância com os resultados obtidos por Mata *et al* (2004). A hiperglicemia pareceu contribuir para aumento da concentração salivar de cálcio (Tabela 2).

Neste estudo, a concentração de glicose foi significativamente maior nos grupos DM1, DM1-A e DM1-B quando comparados ao grupo controle ($P < 0,05$). Vários estudos apontaram esta diferença (Belazi *et al* 1998; López *et al* 2003; Moreira *et al* 2009), e outros não observaram diferenças na concentração salivar de glicose entre diabéticos e não diabéticos (Swanljung *et al*, 1992; Carda *et al* 2006). O aumento da concentração de glicose salivar em adolescentes com DM1 é importante para o controle e acompanhamento da doença. A concentração salivar de glicose pode estar relacionada

com a concentração de glicose no sangue (Belazi *et al* 1998; Iughetti *et al* 1999; Mata *et al* 2004).

Não houve diferenças significantes para a concentração salivar de ureia entre adolescentes com DM1 (grupo DM1) e sem DM1 (grupo controle), de acordo com estudo anterior (Meurman *et al* 1998) e contrariando outros estudos (López *et al* 2003; Carda *et al* 2006). No entanto, nos últimos estudos (López *et al* 2003; Carda *et al* 2006), as concentrações de ureia em indivíduos com DM foram maiores do que nos controles. No presente estudo, a hiperglicemia pareceu contribuir para aumento da concentração salivar de ureia (Tabela 2), com diferença significante entre grupos DM1-B e controle. Dieta hiperproteica e defeitos na excreção de ureia por causas renais podem elevar os valores de uréia em soro, plasma e urina (Searcy *et al* 1964). Sugere-se investigar a relação entre os valores elevados das concentrações salivares de ureia em adolescentes com hiperglicemia, com função renal e composição da dieta.

A diferença significativa na composição salivar e no FSE entre adolescentes com e sem DM1 e a alta prevalência de xerostomia em adolescentes com DM1 sugere aumento do risco à cárie dental e doenças bucais em pacientes com DM1. Além disso, a xerostomia tem mostrado apresentar impacto negativo na qualidade de vida de adolescentes com DM1 (Busato *et al* 2009). No entanto, há carência de trabalhos na literatura que mostrem a prevalência de hiperglicemia e sua associação com composição salivar e xerostomia em adolescentes com DM1, dificultando a comparação direta entre este estudo e outros.

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Tabelas

Tabela 1. Xerostomia da população estudada

Variáveis n (%)		**Grupo DM1 n = 51**	**Grupo Controle n = 51**	***P* valor**
Xerostomia 1 (boca seca)	Sim	27 (53)	8 (16)	<0,001 †
	Não	24 (47)	43 (84)	
Necessidade de bebida	Sim	12 (24)	2 (4)	0,004 †
	Não	39 (76)	49 (96)	
Quantidade de saliva referida	baixa	5 (10)	2 (4)	NS
	Normal	46 (90)	49 (96)	
Dificuldade para engolir	Sim	3 (6)	1 (2)	NS
	Não	49 (94)	50 (98)	
Xerostomia 2	Sim	10 (20)	0 (0)	0,001 †
	Não	41 (80)	51 (100)	
Xerostomia 3	Sim	5 (10)	0 (0)	0,028 †
	Não	46 (90)	51 (100)	

Grupo DM1: adolescentes com DM1, Grupo controle: adolescentes sem DM1
† Teste Exato de Fisher's P ≤ 0,05, NS não-significativo (P > 0,05)

Tabela 2. Composição salivar e xerostomia da população estudada

Variáveis n (%) ou média (DP)		DM1 grupo n = 51	DM1-A n=18	DM1-B n=33	Grupo Controle n = 51	*P* valor
Xerostomia 1	sim	27 (53)	11 (61)	16 (48)	8 (16)	<0,001 [a c] †
	não	24 (47)	7 (39)	17 (52)	43 (84)	0,001[b] †
FSE (mL/min)		0,932 (0,537)	1,140 (0,688)	0,812 (0,361)	1,224 (0,577)	0,003[a] ₸ NS[b] 0,002[c] ₸
Proteínas totais (mg/dL)		218 (386)	139 (67)	262 (460)	239 (144)	0,009[a] ₸ 0,007[b] ₸ NS[c]
Amilase (U/dL)		758 (33)	767 (35)	757 (31)	778 (9)	NS[a b c]
Ureia (mmol/L)		5,340 (2,157)	4,662 (1,565)	5,769 (2,140)	4,957 (2,040)	NS[a b] 0.042[c] ₸
Cálcio (mmol/L)		0,752 (0,496)	0,562 (0,366)	0,803 (0,515)	0,401(0,338)	0,001[a] ₸ NS[b] <0,001[c] ₸
Glicose (mmol/L)		0,174 (0,183)	0,158 (0,154)	0,170 (0,189)	0,098 (0,115)	0,021[a] ₸ 0,024[b] ₸ 0,038[c] ₸

Grupo DM1: adolescentes com DM1, DM1-A: adolescentes com DM1 (GC ≤ 130mg/dL), DM1-B: adolescentes com DM1 (GC > 130mg/dL), Grupo controle: adolescentes sem DM1
FSE (fluxo salivar estimulada) ; ₸ Teste de Mann-Whitney U, † Teste Exato de Fisher's, NS não-significante (P > 0,05)
[a] p valor de Grupo DM1 X grupo controle; [b] p valor de DM1-A X grupo controle; [c] p valor de DM1-B X grupo controle

Impact of hyperglycemia on xerostomia and salivary composition and flow rate of adolescents with type 1 diabetes mellitus

Abstract

Objective: To evaluate the association among hyperglycemia, xerostomia, and salivary flow rate and composition of adolescents with type 1 diabetes mellitus (DM1).

Materials and Methods: A case-control epidemiologic study was performed on adolescents allocated between two groups: DM1 group comprised of 51 with DM1; control group, comprised of 51 non-diabetics. In DM1 group, capillary glucose (CG) values were observed, whereby CG ≤ 130 mg/dL was considered to indicate good glycemic control (DM1-A group) and > 130 mg/dL was considered to indicate hyperglycemia (DM1-B group). Xerostomia was detected by asking a question about the sensation of having “dry mouth”. Salivary flow was evaluated by means of stimulated saliva collection (SSFR). Total protein, amylase, urea, calcium and glucose salivary concentrations were obtained.

Results: A total of 33 (65%) subjects in DM1 group presented hyperglycemia. Xerostomia was indicated by 27 (53%) adolescents in DM1 group in contrast to 8 (16%) subjects in control group ($P < 0.001$). SSFR mean values were 0.932 mL/min in DM1 group, 1.224 mL/min in control group, and 0.812 mL/min in DM1-B, with significant differences between DM1 and control groups, and DM1-B and control groups ($P < 0.05$). Analysis of the biochemical composition of saliva showed that there were significant differences between DM1-B and control group with regard to urea ($P = 0.042$), calcium ($P < 0.001$) and glucose ($P = 0.038$).

Conclusions: Hyperglycemia was a risk factor for SSFR reduction and increased urea and calcium salivary concentrations.

Key words: type 1 diabetes mellitus, flow rate, adolescents, salivary composition, xerostomia, hyperglycemia.

Introduction

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 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).

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 and 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).

Patients with DM1, particularly those who have poor glycemic control, may have decreased salivary flow rate (Guggenheimer and 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.

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.

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 (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).

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).

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).

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.

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%).

Results

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). Thirty-three (65%) adolescents were hyperglycemic (DM1-B group) while 18 (35%) showed good glycemic control (DM1-A group).

The presence of xerostomia 1 (dry mouth) was indicated by 27/51 (53%) subjects in DM1 group and 8/51 (16%) in control group ($P < 0.001$) (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 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. Only DM1 group subjects presented xerostomia 2 (n=10, 10.2%) and xerostomia 3 (n=5, 5.1%). There were significant differences between DM1 group and control group regarding xerostomia 2 ($P = 0.001$) and xerostomia 3 ($P = 0.028$) (Table 1).

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).

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.

Discussion

In the present study, hyperglycemia (CG > 130 mg/dL) was observed in 33 (65%) adolescents with DM1. 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.

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). 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 al*, 2006; von Bültzingslöwen *et al*, 2007). Xerostomia prevalence in elderly diabetes 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 adolescents with DM1 and 0.812 mL/min in hyperglycemic subjects. Both mean values showed significant differences compared with average SSFR in controls (1.224 mL/min). 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 and 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 and Williamson, 2001). In the present study, calcium salivary concentration in DM1 group was significantly higher compared with that of control group, in consonance with previous study (Mata *et al* 2004). Hyperglycemia was associated to an increase in salivary concentration of calcium (Table 2).

In this study, the glucose salivary concentration was significantly higher in the 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. They 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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Tables

Table 1. Xerostomia of the studied population

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 2. Salivary characteristics and 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	sim	27 (53)	11 (61)	16 (48)	8 (16)	<0.001[a c] †
	não	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] ∓ NS[b] 0.002[c] ∓
Total Protein (mg/dL)		218 (386)	139 (67)	262 (460)	239 (144)	0.009[a] ∓ 0.007[b] ∓ 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] ∓
Calcium (mmol/L)		0.752 (0.496)	0.562 (0.366)	0.803 (0.515)	0.401(0.338)	0.001[a] ∓ NS[b] <0.001[c] ∓
Glucose (mmol/L)		0.174 (0.183)	0.158 (0.154)	0.170 (0.189)	0.098 (0.115)	0.021[a] ∓ 0.024[b] ∓ 0.038[c] ∓

DM1-group: adolescents with DM1, DM1-A: adolescents with DM1 (CG ≤ 130mg/dL), DM1-B: adolescents with DM1 (CG > 130mg/dL), Control group: adolescents without DM1
SSFR (stimulated salivary flow rate)
∓ 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; [c] p value of DM1-B X control group

Xerostomia e qualidade de vida: condições de saúde bucal e salivares em adolescentes com *diabetes mellitus* tipo 1

Artigo segue as normas da Revista *Community Dentistry and Oral Epidemiology* disponíveis no site: http://www.wiley.com/bw/submit.asp?ref=0301-5661&site=1

RESUMO

Objetivo. Investigar a influência das condições de saúde bucal e salivares na prevalência da xerostomia com impacto negativo na qualidade de vida (QOL) de adolescentes com *diabetes mellitus* tipo 1 (DM1).

Design do estudo. Estudo transversal com 102 adolescentes, 51 com DM1 e 51 não-diabéticos. A xerostomia foi detectada por questionário e o OHIP-14 foi utilizado para medir seu impacto na QOL. Foram avaliadas as condições de saúde bucal: índices CPOD e Periodontal Comunitário, e manifestações bucais; e as condições salivares: fluxo salivar estimulado, pH, capacidade tampão, concentrações de proteínas totais, amilase, ureia, cálcio e glicose. A regressão logística múltipla avaliou a influência das condições da saúde bucal e salivares na xerostomia e no impacto da xerostomia na QOL de adolescentes com DM1.

Resultados. Condições da saúde bucal e salivares não influenciaram na presença de xerostomia. Na análise bivariada (P = 0,000) e na regressão logística (P = 0,010), houve significativa associação entre DM1 e xerostomia. A regressão logística mostrou associação entre xerostomia (P = 0,005) e QOL, e experiência de cárie (P = 0,033) e QOL.

Conclusão. DM1 foi considerado fator de risco a xerostomia em adolescentes. Experiência de cárie e xerostomia mostraram impactar negativamente na QOL de adolescentes com DM1.

Palavras-chaves. *diabetes mellitus*, xerostomia, qualidade de vida, saliva, índice CPOD, OHIP-14, fluxo salivar, periodonto.

Xerostomia significa uma sensação subjetiva de boca seca (1) e representa um sintoma relatado pelo paciente (2-6). Xerostomia pode resultar da redução da secreção salivar ou ocorrer na presença de fluxo salivar normal (2) Alterações na composição da saliva e na quantidade da saliva podem induzir a xerostomia (7)

O *diabetes mellitus* tipo 1 (DM1) é uma disfunção metabólica caracterizada pela hiperglicemia resultante da deficiência definitiva na secreção de insulina, provocada por doença auto-imune e fatores genéticos (8). O relacionamento entre DM1 e condições de saúde bucal (3,9-17) e condições salivares (9,10,12,13,15,16) tem sido amplamente investigado. A xerostomia (boca seca) é uma das manifestações bucais do DM1 (14,18).

Locker (19) propôs um modelo conceitual da saúde bucal que avalia o impacto da mesma na qualidade de vida (QOL). É um modelo multidimensional para entender as doenças bucais e suas consequências. Em 1997, Slade (20) estudou a possibilidade de avaliar este impacto por meio do *Oral Health Impact Profile* – OHIP-14 (14 questões), uma versão menor que o *Oral Health Impact Profile* – OHIP (49 questões), mantendo confiança, validade e precisão. A relação entre QOL e xerostomia vem sendo estudada em trabalhos recentes (21–27) A xerostomia mostrou ter impacto negativo na QOL de adolescentes com DM1.[27]

A hipótese deste estudo é que a presença de DM1, as condições de saúde bucal e salivares influenciam na prevalência da xerostomia com impacto negativo na QOL de adolescentes.

Materiais e métodos

Pacientes e responsáveis foram informados sobre o objetivo e demais aspectos da pesquisa e assinaram o Termo de Consentimento Livre e Esclarecido. O presente estudo foi aprovado pelo Comitê de Ética em Pesquisa da PUCPR e pela Direção do Hospital de Clínicas do Paraná - UFPR.

População

Estudo epidemiológico caso-controle com 102 adolescentes. Os adolescentes foram alocados em dois grupos: grupo DM1 composto por 51 adolescentes com DM1, acompanhados no Ambulatório de Diabetes do Hospital de Clínicas - Universidade Federal do Paraná, e grupo controle composto por 51 adolescentes não diabéticos, recrutados em escolas públicas de ensino médio. A classificação da ADA (8) foi usada para diagnóstico de DM1 e estabelecida como critério de inclusão do grupo DM1. O critério de inclusão para

grupo controle foi de adolescentes não-diabéticos que não fizeram uso de qualquer fármaco há menos de um mês. Critérios de exclusão para os grupos DM1 e controle foram: presença de condições sistêmicas que pudessem influenciar a fisiologia das glândulas salivares; indivíduos fumantes, etilistas ou usuários de drogas ilícitas; presença de cegueira total (27). Sexo e idade (14-19 anos) foram pareados entre os grupos (DM1 e controle).

Xerostomia

Xerostomia é definida como sensação de boca seca relatada pelo paciente (1). A xerostomia foi detectada pela pergunta: você tem tido sensação de "boca seca" diariamente nos últimos seis meses? (questão A). Respostas "sim" foram consideradas como presença de xerostomia 1. Essa avaliação foi completada pelas perguntas: como você descreve a quantidade de saliva na sua boca? (questão B); você tem dificuldade para engolir a comida? (questão C); e, você precisa de uma bebida para engolir as refeições? (questão D). A xerostomia 2 foi considerada presente quando houve resposta positiva para a questão A e para uma das questões (B, C ou D) relacionadas à xerostomia. Os grupos DM1 e controle foram separados em quatro subgrupos de acordo com a presença de xerostomia: DM1com xerostomia, DM1 sem xerostomia, controle com xerostomia e controle sem xerostomia.

Avaliação da QOL

Avaliação do impacto da xerostomia na QOL foi realizada por meio do questionário OHIP-14 (20). O OHIP-14 foi transculturado para o português, possuindo as mesmas propriedades psicométricas que o instrumento no idioma original (28). Foi solicitado aos pacientes que respondessem o questionário considerando os últimos seis meses. Para calcular o impacto na QOL, foi utilizado o método ponderado padronizado das respostas: nunca-0, raramente-1, às vezes-2, repetidamente-3, sempre-4. Foi atribuído um peso para cada questão (29). O peso de cada questão foi multiplicado pelo valor da respectiva resposta (0, 1, 2, 3 ou 4). Na pontuação final, podiam ser obtidos valores entre 0 e 28 pontos. Quanto maior o valor, maior o impacto negativo da xerostomia na QOL (28). Os valores finais do OHIP-14 foram categorizados da seguinte maneira: 0 – sem impacto; 1-3 – impacto baixo; 4-6 – impacto médio; 7-10 – impacto negativo; 11-16 – alto impacto negativo (29).

Condições da saúde bucal

O exame clínico foi sistemático e ordenado, e qualquer alteração na mucosa bucal foi registrada. O Índice Periodontal Comunitário – IPC foi utilizado para avaliação periodontal. O exame foi realizado por meio de sonda periodontal de ponta esférica. O IPC foi avaliado somando-se os valores dos seis dentes índices (primeiros molares de cada quadrante, incisivo central superior direito, incisivo central inferior esquerdo), podendo o valor total variar de 0 a 24. A experiência de cárie dental foi constatada pelo Índice CPOD (cariado, perdido e restaurado) para dentes. O exame foi realizado com espelho clínico plano. Os critérios de diagnóstico seguiram os propostos pela WHO (30).

Condições salivares

A saliva foi coletada com a utilização de estímulo mastigatório mecânico, por meio de pedaço de látex para garrote estéril de tamanho padronizado (1,5 cm), mastigado continuamente pelo paciente durante 6 minutos. A saliva produzida durante o primeiro minuto de estimulação foi desprezada. Durante os 5 minutos subseqüentes, o paciente expeliu a saliva no interior de um pote coletor universal esterilizado e previamente pesado, numa balança analítica - Marte®, modelo AL 500 (SP – Brasil). A saliva foi coletada no período entre 8:00 horas e 10:00 horas. O fluxo salivar estimulado (FSE) foi avaliado por meio do método gravimétrico, expresso em mL/min (31).

Imediatamente após coleta da saliva, o pH salivar foi avaliado usando pHmetro de bolso da QUIMIS® Q400BD (eletrodo direto) (Diadema - SP/ Brasil). A capacidade tampão da saliva (CTS) foi determinada por meio da titulometria com 1 mL de saliva adicionado a 3 mL de HCl 5 mmol/L. Após 10 minutos, foi verificado o pH final com pHmetro de bolso (32). Antes de submeter as amostras de saliva às provas bioquímicas, estas foram centrifugadas (3.000 g por 10 min). Concentrações salivares de proteínas totais e cálcio foram determinadas pelo método colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de amilase foi determinada pelo método cinético colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de ureia foi determinada pelo método enzimático colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de glicose foi determinada pelo método enzimático colorimétrico (Kits BIOCLIN®/Belo Horizonte - MG/ Brasil). Os testes bioquímicos salivares foram realizados em triplicata.

Análise dos dados

A análise dos dados foi realizada em quatro etapas usando o *SPSS versão 15.0 for Windows*. Análise de normalidade usada foi o Teste de Kolmogorov-Smirnov e o teste de Levene avaliou a homogeneidade de variância.

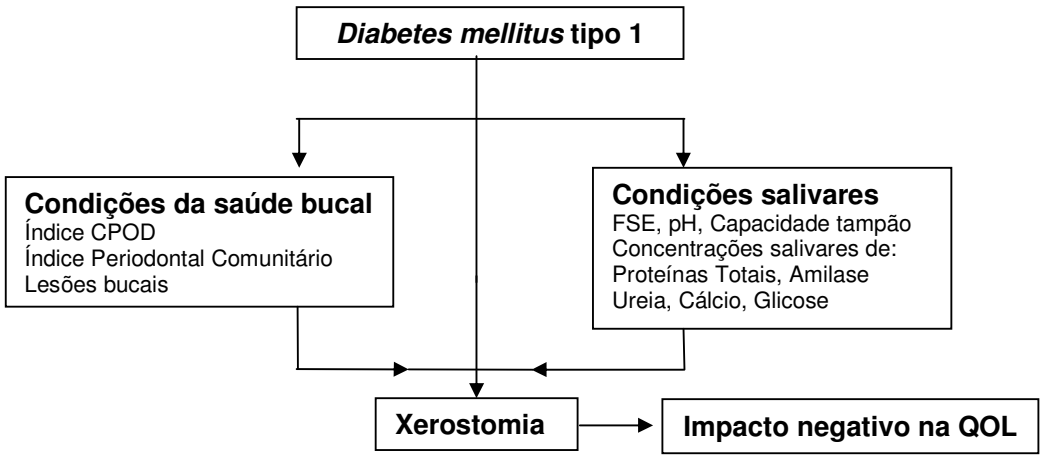
A primeira etapa consistiu na realização das análises bivariadas considerando a presença de DM1 como variável dependente, utilizando os testes Mann-Whitney U e Exato de Fisher's. O nível de significância adotado foi $P \leq 0,05$ e IC 95%.

A segunda etapa realizou análises bivariadas considerando a presença de xerostomia 1 entre os grupos DM1 e controle, como variável dependente, usando o Teste Kruskal Wallis, considerando estatisticamente significativo $P \leq 0,05$ e IC 95%.

A terceira etapa foi realizada com modelo estatístico de regressão logística múltipla para investigar a probabilidade da ocorrência da xerostomia na presença de DM1, condições de saúde bucal e salivares (Figura 1). A variável xerostomia 1 foi usada como variável dependente. Ausência de xerostomia foi codificada em 0 e presença de xerostomia em 1. Variáveis independentes foram: presença de DM1, condições de saúde bucal e salivares (Figura 1).

A quarta etapa foi realizada com modelo estatístico de regressão logística múltipla para investigar a probabilidade do impacto negativo na QOL na presença de xerostomia, condições de saúde bucal e salivares (Figura 1), em dois momentos. A variável OHIP-14 (pontos) foi usada como variável dependente, tomando a mediana como ponto de corte entre ter impacto negativo, codificado com 1, e não ter impacto negativo, codificado com 0. No momento 1, a população estudada foi de adolescentes (n=102) e as variáveis independentes foram: presença de DM1, presença de xerostomia 1, condições de saúde bucal e salivares (Figura 1). No momento 2, foram analisados os adolescentes com DM1 (n=51) e as variáveis independentes foram: presença de xerostomia 1, condições de saúde bucal e salivares (Figura 1).

Figura 1. Modelo teórico de determinação da xerostomia e impacto negativo na QOL.



Resultados

A média de idade foi de 17 ± 1,4 anos (14-19), com a presença de 27 indivíduos do sexo feminino e 24 do sexo masculino nos dois grupos (DM1 e controle). A presença do DM1 mostrou influenciar na maior prevalência de xerostomia, piorando condições de saúde bucal e provocando alterações nas condições salivares (Tabela 1). Experiência de cárie e concentração salivar de glicose, amilase e ureia pareceram não estar associadas a xerostomia na análise bivariada (Tabela 2). A regressão logística aplicada aos dados dos 102 adolescentes (momento 1) apontou significativa associação entre DM1 e xerostomia (P = 0,010). A regressão logística aplicada aos dados dos 51 adolescentes com DM1 (momento 2) mostrou associação entre xerostomia e QOL (P = 0,005), e experiência de cárie e QOL (P = 0,033) (Tabela 3).

Na avaliação bivariada considerando o DM1 como variável dependente, houve diferença estatística entre grupo DM1 e grupo controle para as variáveis xerostomia 1 (P = 0,000) e xerostomia 2 (P = 0,001). As diferenças entre grupo DM1 e grupo controle para as condições de saúde bucal ocorreram para o Índice CPOD (P = 0,020), IPC (P = 0,000) e lesões bucais (P = 0,007). Nas condições salivares, houve diferença estatística entre grupo DM1 e grupo controle para: FSE (P = 0,003), pH (P = 0,000), CTS (P = 0,000), concentrações salivares de proteínas totais (P = 0,009), cálcio (P = 0,001) e glicose (P = 0,021). Valores médios de OHIP-14 não mostraram ter diferença significante entre os grupos DM1 e controle (Tabela 1).

A Tabela 2 mostra a análise bivariada considerando xerostomia como variável dependente. Nas condições de saúde bucal, IPC (P = 0,000) e lesões bucais (P = 0,046) mostraram ter diferença estatística entre os quatro grupos. Nas condições salivares houve diferença entre os grupos para as variáveis: FSE (P = 0,043), pH (P = 0,000), CTS (P = 0,000), concentrações salivares de proteínas totais (P = 0,019) e cálcio (P = 0,004). Houve diferença entre os grupos para os valores de OHIP-14 (P = 0,002). Destaca-se o valor médio do OHIP-14 no grupo DM1 (7,0), representando impacto negativo da xerostomia na QOL.[29]

A Tabela 3 mostra o resultado das análises de regressão logística realizadas. Na terceira etapa da análise estatística, as concentrações de amilase e ureia salivar não foram incluídas na regressão uma vez que não houve diferenças estastíticas entre grupos nas análises bivariadas (Tabelas 1 e 2). O *Model Chi-square* do modelo logístico foi de 25.160

(10df; P > 0,05) e, sem a constante, foi de 35.345 (10df; P > 0,05). O Teste Nagelkerk R^2 ajustado alcançou 30,2% e sem a constante 39%. Somente a presença de DM1 foi preditiva para a presença de xerostomia com P = 0,037 (com a constante) e P = 0,010 (sem a constante) (Tabela 3).

Na quarta etapa da análise estatística, momento 1, o modelo da regressão logística com o grupo de adolescentes (n = 102) com impacto negativo na QOL (pontos OHIP-14) apontou não haver resultados significativos. No momento 2, o resultado da regressão logística com o grupo de adolescentes com DM1 (n = 51) com impacto negativo na QOL (pontos OHIP-14) apontou que o *Model Chi-square* do modelo logístico foi de 18.153 (12df; P > 0,05) e, sem a constante, 17.608 (12df; P > 0,05). O Teste Nagelkerk R^2 com o ajuste mostrou 40% (38,9% sem a constante). As variáveis independentes xerostomia (P = 0,004; sem a constante P = 0,005) e Índice CPOD (P = 0,030; sem a constante P = 0,033) foram preditivas no impacto negativo na QOL (Tabela 3).

Discussão

Neste estudo, o DM1 mostrou influenciar na maior prevalência de xerostomia e pareceu não ter impacto negativo na QOL de adolescentes comparado com adolescentes sem diabetes. A presença de DM1 foi significativa para a piora das condições de saúde bucal e alterações nas condições salivares. Experiência de cárie e concentrações salivares de amilase, ureia e glicose pareceram não estar associadas à xerostomia. Por outro lado, a xerostomia e a experiência de cárie mostraram associação com a QOL.

Xerostomia é uma manifestação importante na saúde bucal em pessoas com diabetes (14,18,27) e, quando presente, causa problemas clínicos e sociais (7), com impacto negativo na QOL (27). Neste estudo, a prevalência de xerostomia foi de 53% para adolescentes com DM1 em consonância com estudo que obteve 54% (22) em adultos com diabetes tipo 2. Apenas adolescentes com DM1 (n=10; 20%) responderam positivamente a duas questões relacionadas à xerostomia (xerostomia 2), o que enfatiza a influência do DM1 na maior prevalência de xerostomia. As diferenças estatísticas entre a prevalência de xerostomia 1 e xerostomia 2 em adolescentes com e sem DM1 mostraram a importância desta manifestação entre adolescentes com DM1. Ressaltamos as limitações de estudos na literatura sobre a prevalência de xerostomia em adolescentes com DM1 para confrontar com achados deste estudo.

A experiência de cárie dental foi significativamente maior em adolescentes com DM1 comparado aos não-diabéticos. Alguns trabalhos também demonstraram diferenças na experiência de cárie entre adolescentes com e sem DM1 (3,9-11,33), enquanto outros não observaram estas diferenças (12-14). No presente estudo, as condições periodontais foram prejudicadas na presença do DM1, da mesma forma que em trabalhos anteriores (9,11,12,15,33). Mesmo sendo baixa na adolescência (33), a prevalência de manifestações na mucosa bucal foi maior na presença do DM1, o que está de acordo com o estudo de Belazi *et al* (16).

No presente estudo, a presença de DM1 foi significativa para a redução do FSE de adolescentes, em concordância com trabalhos anteriores (10,12) e discordando de outros trabalhos (13,15), onde não houve diferença no FSE entre adolescentes com e sem DM1. A presença do DM1 também mostrou provocar alterações no pH (15) e na CTS (15,16) entre adolescentes com e sem DM1. Neste estudo, o grupo DM1 apresentou maior pH salivar e maior CTS comparado ao grupo controle. Contudo ressalta-se que Swanlijung *et al.* (13) não encontraram diferenças no pH salivar e na CTS entre pacientes com e sem DM1. Neste estudo, houve diferenças nas concentrações salivares de proteínas totais, cálcio e glicose entre pacientes com e sem DM1, de acordo com trabalhos anteriores (9,12) Outros trabalhos não encontraram diferenças entre grupos com e sem DM1 para concentrações salivares de glicose (13), cálcio (9), e proteínas totais (16).

A experiência de cárie pareceu não estar relacionada com a xerostomia, o que foi apontado também por Moore *et al.* (3) em 2001. A QOL, mensurada pelos valores médios do OHIP-14, mostrou relacionar-se com a xerostomia, na avaliação bivariada entre os grupos (Tabela 2). Esta relação também foi encontrada em trabalhos anteriores (4-6,21-27). Neste estudo, na análise bivariada, as alterações na quantidade (FSE) e na composição bioquímica da saliva (proteínas totais e cálcio) estiveram relacionadas à presença de xerostomia.

O DM1 foi confirmado como fator de risco à xerostomia para adolescentes. No modelo teórico da determinação da xerostomia deste estudo, não ter DM1 contribuiria para diminuir a probabilidade de ocorrer a xerostomia. Contudo, há necessidade de outros estudos com variáveis preditoras distintas das avaliadas neste estudo. A regressão logística não demonstrou que condições de saúde bucal e salivares têm influência na xerostomia, o que contradiz o modelo teórico da determinação da xerostomia (Figura 1). Este resultado

contrapõe resultados encontrados em idosos, onde saúde bucal e xerostomia estiveram relacionadas (21). Atkison *et al.*(34) apontaram que a xerostomia pode estar relacionada com a falta de hidratação ou condições sistêmicas. Outros trabalhos relacionaram a xerostomia ao mau controle do DM1 (35), a fatores psicológicos (36), ao DM1 (27) e a fatores psicológicos (37).

A regressão logística com os adolescentes (n = 51) demonstrou que a xerostomia foi um fator de risco com impacto negativo na QOL. Outros estudos que avaliaram adultos (5,22,24) e idosos (4,6,21,26) também demonstraram esta relação. Não apresentar xerostomia colaboraria para diminuir o impacto negativo na QOL de adolescentes. Neste estudo, a presença de DM1 pareceu não impactar negativamente na QOL de adolescentes, contrariando os resultados de Sandberg & Wikblad (22), que estudaram adultos com diabetes tipo 2.

A experiência de cárie (Índice CPOD) e a xerostomia mostraram ser preditivas para a QOL de adolescentes com DM1, o que concorda com os resultados obtidos em adultos jovens com DM1 (23). Diminuir a experiência de cárie (Índice CPOD) concorreria para aumentar a probabilidade de ocorrer impacto negativo na QOL de adolescentes com DM1.

Conclusão

O DM1 em adolescentes é um fator de risco à xerostomia e prejudica a saúde bucal (23), tornando-se um diagnóstico importante em saúde pública (4). Na ocorrência de xerostomia, há necessidade de investigação contínua do complexo relacionamento entre condições clínicas e impacto negativo no comportamento (19). O modelo de identificação da xerostomia deve ser explorado (5), com a inclusão de outras variáveis, tais como fatores sócio-econômicos e saúde geral.

Experiência de cárie e xerostomia mostraram impactar negativamente na QOL de adolescentes com DM1. A avaliação do impacto negativo de condições clínicas e sintomas de doenças sistêmicas na QOL deve ser considerada por profissionais e serviços de saúde (25). A prevenção da cárie dental e a promoção de saúde bucal devem ser advogadas pelos profissionais de saúde que realizam acompanhamento de pacientes com DM1, independente da faixa etária. Neste grupo de risco, há necessidade de desenvolvimento de políticas públicas para o acompanhamento e tratamento da xerostomia na adolescência, evitando a piora desta complicação e impacto negativo na QOL.

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TABELAS

Tabela 1. Análise bivariada da população do estudo, considerando o DM1 como variável dependente

Variáveis n (%) ou média (DP)		**Grupo DM1 n = 51**	**Grupo controle n = 51**	**Valor P**
Xerostomia				
Xerostomia 1,	sim	27 (53)	8 (16)	0,000 ₸
	não	24 (47)	43 (84)	
Xerostomia 2,	sim	10 (20)	0 (0)	0,001 ₸
	não	41 (80)	51 (100)	
Condições de saúde bucal				
Ïndice CPOD		3,33 (3,70)	1,54 (2,12)	0,020 †
IPC		1,83 (1,85)	0,2 (0,84)	0,000 †
Lesões bucais,	sim	11 (22)	2 (4)	0,007 ₸
	não	40 (78)	49 (96)	
Condições salivares				
FSE		0,932 (0,537)	1,224 (0,577)	0,003 †
pH		7,76 (0,55)	7,41 (0,37)	0,000 †
CTS		4,71 (0,87)	3,74 (1,05)	0,000 †
Proteínas totais (mg/dL)		218 (386)	239 (144)	0,009 ₸
Amilase (U/dL)		758 (33)	778 (9)	NS
Ureia (mmol/L)		5,340 (2,157)	4,957 (2,040)	NS
Cálcio (mmol/L)		0,752 (0,496)	0,401(0,338)	0,001 ₸
Glicose (mmol/L)		0,174 (0,183)	0,098 (0,115)	0,021 ₸
Qualidade de Vida				
OHIP-14		5,2 (4,6)	4,3 (3,4)	NS

DM1 *diabetes mellitus* tipo 1
FSE (fluxo salivar estimulado), CTS (capacidade tampão salivar)
Ïndice CPOD (cariado, perdido e restaurado), IPC (Índice Periodontal Comunitário)
NS P > 0,05, † Teste Mann-Whitney U, ₸ Teste Exato de Fisher's

Tabela 2. Análise bivariada da população de estudo, considerando a xerostomia como variável dependente

Variáveis n (%) ou média (DP)	Grupo DM1 Com xerostomia n=27	Grupo DM1 Sem xerostomia n=24	Grupo controle Com xerostomia n=8	Grupo controle Sem xerostomia n=43	Valor P
Condições de saúde bucal					
Índice CPOD	2,81 (2,98)	4,58 (4,80)	3,13 (3,72)	1,42 (1,74)	NS
IPC	2,04 (1,99)	1,63 (1,66)	0,88 (1,81)	0,07 (0,33)	0,000 †
Lesões bucais, n (%)	4 (15) 23 (85)	7 (29) 17 (71)	0 (0) 8 (100)	2 (5) 41 (95)	0,046 †
Condições salivares					
FSE	1,037 (0,561)	0,885 (0,508)	1,345 (0,528)	1,161 (0,599)	0,043 †
pH	7,9 (0,44)	7,73 (0,61)	7,19 (0,09)	7,45 (0,40)	0,000 †
CTS	4,99 (0,81)	4,63 (0,78)	4,20 (1,00)	3,63 (1,09)	0,000 †
Proteínas totais (mg/dL)	164 (99)	139 (82)	201 (206)	239 (130)	0,019 †
Amilase (U/dL)	780 (27)	750 (39)	781 (4)	777 (10)	NS
Ureia (mmol/L)	4,967 (2,235)	5,407 (1,738)	4,036 (1,565)	5,085 (2,065)	NS
Cálcio (mmol/L)	0,600 (0,431)	0,796 (0,493)	0,313 (0,210)	0,424 (0,361)	0,004 †
Glicose (mmol/L)	0,181 (0,226)	0,144 (0,126)	0,100 (0,128)	0,098 (0,113)	NS
Qualidade de Vida					
OHIP-14	7,0 (4,8)	2,8 (2,3)	3,4 (1,7)	4,3 (3,5)	0,002 †

DM1(*diabetes mellitus* tipo 1)
FSE (fluxo salivar estimulado), CTS (capacidade tampão salivar)
Índice CPOD (cariado, perdido e restaurado), IPC (Índice Periodontal Comunitário)
NS P > 0,05, † Teste Kruskal Wallis

Tabela 3. Regressão logística múltipla para população estudada

Variável dependente * [a] Xerostomia 1 (ausente=0 e presente=1)						
Variável Independente	**B**	**SE**	**Wald**	**P valor**	**Exp (B)**	**IC 95%**
Presença DM1	-1,515	0,727	1,000	0,037	0,219	0,062 ; 0,684
Constante	-0,825	5,100		0,872	0,438	
Presença DM1	-1,581	0,613	9,694	0,010	0,206	0,062 ; 0,684
Variável dependente ** [b] OHIP-14 (< 4 pontos = 0 e ≥ 4 pontos = 1)						
Variável Independente	**B**	**SE**	**Wald**	**P valor**	**Exp (B)**	**IC 95%**
Índice CPOD	0,267	0,123	7,000	0,030	1,306	1,021 ; 1,644
Xerostomia	-2,495	0,867	7,921	0,004	0,082	0,018 ; 0,487
Constante	-0,184	14,808	1,000	0,990	0,832	
Índice CPOD	0,259	0,122	8,000	0,033	1,295	1,021 ; 1,644
Xerostomia	-2,367	0,841	8,286	0,005	0,094	0,018 ; 0,487

[a] Variáveis P > 0,05: FSE, Índice CPOD, IPC, pH, CTS, Proteína, Calcio, Glicose, e Lesões bucais
[b] Variáveis P > 0,05: FSE, IPC, pH, CTS, Proteína, Calcio, Glicose, e Lesões bucais
IC – Intervalo de confiança
* n = 102 adolescentes
** n = 51 adolescentes DM1 (*diabetes mellitus* tipo 1)

Xerostomia and quality of life: oral health and salivary conditions in adolescents with type 1 diabetes mellitus

Abstract

Objective. To investigate the influence of oral health and salivary conditions on the prevalence of xerostomia with negative impact on the quality of life (QOL) of adolescents with type 1 diabetes mellitus (DM1).

Study Design. A cross-sectional study was performed with 102 adolescents, 51 with DM1 and 51 non-diabetics. Xerostomia was detected using a questionnaire and OHIP-14 was used to measure its impact on QOL. The oral health conditions were assessed: DMF and Community Periodontal indices, and oral manifestations; as were the salivary conditions: stimulated salivary flow, pH, buffer capacity, total protein, amylase, urea, calcium and glucose salivary concentrations. Multiple logistic regression was used to evaluate the influence of oral health and salivary conditions on xerostomia and on the impact of xerostomia on the QOL of adolescents with DM1.

Results. Oral health and salivary conditions did not have an influence in the presence of xerostomia. Bivariate analysis (P = 0.000) and logistic regression (P = 0.010) showed a significant association between DM1 and xerostomia. Logistic regression showed association between xerostomia (P = 0.005) and QOL, and caries experience (P = 0.033) and QOL.

Conclusions. DM1 was considered to be a risk factor for xerostomia in adolescents. Caries experience and xerostomia showed to have a negative impact on the QOL of adolescents with DM1.

Key words: diabetes mellitus, xerostomia, quality of life, saliva, DMF index, OHIP-14, salivary flow, periodontal.

Xerostomia is defined as a subjective sensation of having a dry mouth (1) and is a symptom reported by the patient (2-6). Xerostomia can result from a reduction in saliva secretion, altough it may occur in spite of the presence of normal saliva flow rate (2). Both alterations in saliva composition and in the quantity of saliva may play a role in the induction of xerostomia (7).

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 (8). The relationship between DM1 and oral health conditions (3,9-17) and salivary conditions (9,10,12,13,15,16) has been widely investigated. Xerostomia (dry mouth) is one of the oral manifestations of DM1 (14,18).

Locker (19) proposed a conceptual model of oral health that evaluates its impact on quality of life (QOL). It is a multidimensional model for understanding oral diseases and their consequences. In 1997, Slade (20) studied the possibility of evaluating this impact through the Oral Health Impact Profile – OHIP-14 (14 questions), a smaller version than the Oral Health Impact Profile – OHIP (49 questions), maintaining confidence, validity, and accuracy. The relationship between QOL and xerostomia has been studied in recent research (21–27). Furthermore, xerostomia was shown to have a negative impact on the QOL of adolescents with DM1 (27).

The hypothesis of this study was that the presence of DM1, as well as oral health and salivary conditions, influenced the prevalence of xerostomia with negative impact on QOL of adolescents.

Material and methods

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. This study was approved by the Research Ethics Committee of the Pontifícia Universidade Católica do Paraná and by the Management of the Paraná Federal University Teaching Hospital.

Population

A case-control epidemiologic study was performed on adolescents, allocated between two groups: DM1 group comprised of 51 adolescents with DM1 (DM1 group), who receive follow-up at the Diabetes Outpatients Department of the Paraná Federal University Teaching Hospital, and control group comprised of 51 non-diabetic subjects who were recruited from public high schools. DM1 diagnosis using the ADA (8) 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 the salivary gland physiology; psychotropic drugs users, smokers or illicit drugs users and alcohol users (27). Sex and age (14-19 years) were paired between the groups (DM1 and control).

Xerostomia

Xerostomia was defined as a dry mouth sensation, reported by the subject.[1] Xerostomia was detected by asking: have you had a "dry mouth" sensation every day for the last six months? (question A). If the answer was "yes", xerostomia 1 was considered to be present. 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). Xerostomia 2 was considered to be present when there was a positive answer to question A and to one of the other questions (B, C or D) related to xerostomia. Groups DM1 and control were separated into four sub-groups according to the presence of xerostomia: DM1 group with xerostomia, DM1 group without xerostomia, control group with xerostomia and control group without xerostomia.

QOL evaluation

Evaluation of the impact of xerostomia on QOL was performed using the OHIP-14 questionnaire (20). The OHIP-14 was translated to Portuguese, maintaining the same psychometric properties as the instrument has in its original language (28). Patients were asked to answer the questionnaire considering the previous six-month period. In order to calculate the impact on QOL the standardized weighted method was used for the answers: never-0, rarely-1, sometimes-2, repeatedly-3, always-4. A weight was attributed to each question.[29] The weight of each question was multiplied by the value of the respective answer (0, 1, 2, 3 or 4). The final score could be between 0 and 28 points. The higher the score, the greater the negative impact of xerostomia on QOL.[28] The final OHIP-14 values were categorized as follows: 0 – no impact; 1-3 – low impact; 4-6 – medium impact; 7-10 – negative impact; 11-16 – high negative impact (29).

Oral health conditions

The clinical examination was systematic and ordered, and any alteration to oral mucous membrane was recorded. The Community Periodontal Index – CP was used for periodontal evaluation. The examination was performed using a periodontal probe with a spherical tip. The CP index was evaluated by adding together the values of the six index teeth (first molars in each quadrant, right upper central, and left mandibular central), whereby the total value could vary between 0 and 24. Dental caries experience was rated using the DMF index (decayed, missing or filled) for teeth. The examination was performed using a flat clinical mirror. The criteria for diagnosis followed those proposed by the WHO (30).

Salivary conditions

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 salivary flow rate (SSFR) was evaluated by mean of the gravimetric method and expressed in mL/min (31).

Immediately following saliva collection the salivary pH was assessed using a QUIMIS® Q400BD pocket pH meter (direct electrode) (Diadema - SP/ Brazil). Buffer capacity (BC) was determined by titration with 3 mL of HCl 5 mmol/L added to 1 mL of saliva. After 10 minutes the final pH value was measured using a pocket pH meter (direct electrode) (32). The saliva samples were centrifuged (3.000 g for 10 min) before being submitted to the biochemical tests. Total protein and calcium salivary concentrations were determined using the colorimetric method (LABTEST® kits/Vista Alegre - MG/ Brazil). Amylase concentration was determined using the kinetic colorimetric method (LABTEST® kits/Vista Alegre - MG/ Brazil). Urea concentration was determined using the enzymatic colorimetric method (LABTEST® kits/Vista Alegre - MG/ Brazil). Glucose was determined by the enzymic colorimetric method (BIOCLIN® kits/Belo Horizonte-MG/Brazil). The biochemical salivary tests were performed three times.

Statistical analysis

Data analysis was performed in four stages using SPSS version 15.0 for Windows. Normality analysis was performed using the Kolmogorov-Smirnov test, and Levene test was used to analyse variance homogeneity.

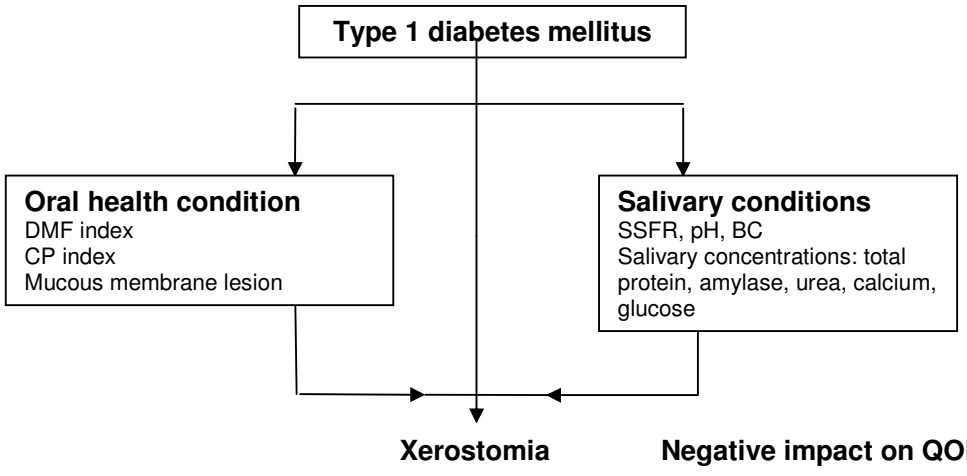
The first stage consisted of performing the bivariate analyses considering the presence of DM1 as a dependent variable, using the Mann-Whitney U test and Fisher's Exact test. The level of significance was set at $P \leq 0.05$ and CI 95%.

In the second stage, bivariate analysis was performed considering the presence of xerostomia 1 in groups DM1 and control as a dependent variable, using the Kruskal Wallis test, whereby statistical significance was considered to be $P \leq 0.05$ and CI 95%.

The third stage was performed using a multiple logistic regression statistical model to investigate the probability of the occurrence of xerostomia in the presence of DM1, and according to oral health and salivary conditions (Figure 1). The xerostomia 1 variable was used as a dependent variable. Absence of xerostomia was coded as 0 and presence of xerostomia was coded as 1. Independent variables were: presence of DM1, oral health and salivary conditions (Figure 1).

The fourth stage involved the use of a multiple logistic regression statistical model to investigate the probability of the negative impact on QOL in the presence of xerostomia and according to oral health and salivary conditions (Figure 1), at two different moments. The OHIP-14 (points) variable was used as a dependent variable, taking the median as the cut-off point between having negative impact, coded as 1, and not having negative impact, coded as 0. In moment 1, the adolescent population (n=102) was studied and the independent variables were: presence of DM1, presence of xerostomia 1, oral health and salivary conditions (Figure 1). In moment 2, the adolescents with DM1 (n=51) were analysed and the independent variables were: presence of xerostomia 1, oral health and salivary conditions (Figure 1).

Figure 1. Theoretical model for determining xerostomia and negative impact on QOL.



Results

Average age was 17 ± 1.4 (14-19), with the presence of 27 female subjects and 24 male subjects in both groups (DM1 and control). The presence of DM1 was shown to influence the higher prevalence of xerostomia, worsening oral health conditions and inducing alterations to the salivary conditions (Table 1). Caries experience and the glicose, amylase and urea salivary concentrations did not show to be associated with xerostomia in the bivariate analysis (Table 2). The logistic regression applied to the data of the 102 adolescents (moment 1) indicated significant association between DM1 and xerostomia (P = 0.010). The logistic regression applied to the data of the 51 DM1 adolescents showed association between xerostomia and QOL (P = 0.005), and caries experience and QOL (P = 0.033) (Table 3).

In the bivariate evaluation considering DM1 as a dependent variable there was statistical difference between DM1 group and control group in relation to xerostomia 1 (P = 0.000) and xerostomia 2 (P = 0.001). Regarding oral health conditions, there were statistical differences for DMF index (P = 0.020), CP index (P = 0.000) and oral lesions (P = 0.007) between DM1 group and control group. Regarding salivary conditions, there were statistical differences between DM1 group and control group in relation to: SSFR (P = 0.003), pH (P = 0.000), BC (P = 0.000), total protein (P = 0.009), calcium (P = 0.001) and glucose (P = 0.021) total salivary concentrations. Average OHIP-14 values did not show to have a significant difference between DM1 group and control group (Table 1).

Table 2 shows the bivariate analysis considering xerostomia as a dependent variable. Regarding oral health conditions, the CP index (P = 0.000) and oral lesions (P = 0.046) showed statistical differences between the four groups. With regard to salivary conditions, there were statistical differences between the groups in relation to the following variables: SSFR (P = 0.043), pH (P = 0.000), CTS (P = 0.000), total protein (P = 0.019) and calcium (P = 0.004) salivary concentrations. There was a statistical difference between the groups in relation to the OHIP-14 values (P = 0.002). The average OHIP-14 value in DM1 group (7.0) represents negative impact of xerostomia on QOL (29).

Table 3 shows the results of all the logistic regression analyses performed. Salivary amylase and urea concentrations were not included in the regression since there were not statistical differences between groups in the bivariate analyses (Tables 1 and 2). In the third stage of the statistical analysis, the Model Chi-square of the logistic model was 25.160

(10df; P > 0.05), and without the constant it was 35.345 (10df; P > 0.05). The adjusted Nagelkerk R^2 test reached 30.2%, and 39% without the constant. Only the presence of DM1 was predictive of the presence of xerostomia, whereby P = 0.037 (with the constant) and P = 0.010 (without the constant) (Table 3).

In moment 1 of the fourth stage of the statistical analysis, the logistic regression model with the group of adolescents (n = 102) with negative impact on QOL (OHIP-14 points) did not indicate significant results. In moment 2, the result of the logistic regression with the group of adolescents with DM1 (n = 51) with negative impact on QOL (OHIP-14 points) indicated that the Model Chi-square of the logistic model was 18.153 (12df; P > 0.05), and 17.608 without the constant (12df; P > 0.05). The adjusted Nagelkerk R^2 test showed 40% (38.9% without the constant). The independent variables xerostomia (P = 0.004; without the constant P = 0.005) and DMF index (P = 0.030; without the constant P = 0.033) were predictive of the negative impact on QOL (Table 3).

Discussion

In the present study, DM1 was shown to influence higher xerostomia prevalence and appeared not to have a negative impact on the QOL of adolescents when compared with adolescents without diabetes. DM1 presence was significant for the worsening of oral health conditions and alterations in salivary conditions. Caries experience and salivary concentrations of amylase, urea and glucose do not appear to be associated with xerostomia. Conversely, xerostomia and caries experience showed to have association with QOL.

Xerostomia is an important oral health manifestation in subjects with diabetes (14,18,27) and, when present, causes clinical and social problems (7), with negative impact on the QOL (27). In this study, xerostomia prevalence was 53 % in adolescents with DM1, which is in consonance with a study that obtained 54% (22) in adults with type 2 diabetes. Only adolescents with DM1 (n=10; 20%) replied positively to two questions related to xerostomia (xerostomia 2), which emphasizes the influence of DM1 on higher xerostomia prevalence. The statistical differences between the prevalence of xerostomia 1 and xerostomia 2 in adolescents with and without DM1 demonstrated the importance of this manifestation in adolescents with DM1. We highlight the limitations of studies in the literature on xerostomia prevalence in adolescents with DM1 to compare with the findings of this study.

Dental caries experience was significantly greater in adolescents with DM1 compared with non-diabetics. Some studies have also demonstrated differences in caries experience among adolescents with and without DM1 (3,9-11,33), whilst others have not observed these differences (12-14) In the present study, the periodontal conditions were impaired in the presence of DM1, in the same way as in previous studies (9,11,12,15,33). Even though it is low in adolescence (33) the prevalence of oral lesions was higher in the presence of DM1, according to the study performed by Belazi et al (16).

In the present study, DM1 presence was significant for SSFR reduction in adolescents, in agreement with some previous studies (10,12) and in contrast to others (13,15) in which there was no difference in SSFR between adolescents with and without DM1. The presence of DM1 has also been shown to induce pH alterations (15) and alterations to saliva buffer capacity (15,16) among adolescents with and without DM1. In this study, DM1 group presented higher salivary pH and greater BC compared with control group. However, Swanlijung et al (13) did not find differences in salivary pH or in BC among patients with and without DM1. In the present study, there were differences in the salivary concentrations of total proteins, calcium and glucose among patients with and without DM1, in agreement with previous studies (9,12). Other studies did not show any differences between groups with and without DM1 regarding glucose (13), calcium (9), and total proteins (16) salivary concentrations.

Caries experience appeared not to be related to xerostomia, which was also indicated by Moore et al (3). QOL, measured according to the average OHIP-14 values, showed itself to be related to xerostomia in the bivariate evaluation between the groups (Table 2). This relation has also been found in previous studies (4-6,21-27) In this study, alterations in the quantity (SSFR) and in the biochemical composition of the saliva (total proteins and calcium) were related to the presence of xerostomia.

DM1 was confirmed as a xerostomia risk factor for adolescents. In the theoretical model used for determining xerostomia in this study, absence of DM1 would appear to contribute to reducing the probability of the occurrence of xerostomia. However, other studies with predictive variables different from those evaluated in this study should be performed. The logistic regression did not demonstrate that oral health and salivary conditions influence xerostomia, which contradicts the theoretical model of xerostomia determination (Figure 1). This result is in contrast to results found in elderly subjects in

which oral health and xerostomia were related (21). Atkison et al (34) indicated that xerostomia may present a relationship with the lack of hydration or systemic conditions. Other studies have related xerostomia to the bad control of DM1 (35), psychological factors (36), and to DM1 (27) and psychological factors (37).

The logistic regression with the DM1 adolescents (n = 51) demonstrated that xerostomia was a risk factor with negative impact on QOL. Other studies that evaluated adults (5,22,24) and elderly subjects (4,6,21,26) have also demonstrated this relationship. Absence of xerostomia would appear to collaborate towards reducing the negative impact on adolescents QOL. In this study, the presence of DM1 did not show to impact negatively on adolescents QOL, in contrast to the results found by Sandberg & Wikblad (22), who studied adults with type 2 diabetes.

Caries experience (DMF index) and xerostomia showed themselves to be predictive of the QOL of adolescents with DM1, and this is in agreement with results obtained in young adults with DM1 (23). Decrease in caries experience (DMF index) would appear to contribute to increasing the probability of the occurrence of negative impact on the QOL of adolescents with DM1.

Conclusions

DM1 in adolescents is a risk factor for xerostomia and is prejudicial to oral health (23). Thus, its diagnosis becomes important for public health (4). When xerostomia occurs the need exists for continuous investigation into the complex relationship between clinical conditions and negative impact on behaviour (19). The xerostomia identification model must be explored (5), with the inclusion of other variables, such as socio-economic and general health factors.

Caries experience and xerostomia showed to have a negative impact on the QOL of adolescents with DM1. Health professionals and health services should take into consideration the evaluation of the negative impact of clinical conditions and symptoms of systemic illnesses on QOL (25). Dental caries prevention and oral health promotion should be advocated by health professionals who monitore patients with DM1, regardless of the age group. In this risk group, there is a need to develop public policies on accompanying and treating xerostomia in adolescents, so as to avoid the worsening of this complication and negative impact on QOL.

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TABLES

Table 1. Bivariate analysis of studied population considering type 1 diabetes mellitus (DM1) as dependent variable

Variables n (%) or mean (SD)		**DM1 group n = 51**	**Control group n = 51**	**P value**
Xerostomia				
Xerostomia 1,	yes	27 (53)	8 (16)	0.000 ∓
	no	24 (47)	43 (84)	
Xerostomia 2,	yes	10 (20)	0 (0)	0.001 ∓
	no	41 (80)	51 (100)	
Oral health conditions				
DMF index		3.33 (3.70)	1.54 (2.12)	0.020 †
CPI		1.83 (1.85)	0.2 (0.84)	0.000 †
Oral lesions,	yes	11 (22)	2 (4)	0.007 ∓
	no	40 (78)	49 (96)	
Salivary conditions				
SSFR		0.932 (0.537)	1.224 (0.577)	0.003 †
pH		7.76 (0.55)	7.41 (0.37)	0.000 †
BC		4.71 (0.87)	3.74 (1.05)	0.000 †
Total protein (mg/dL)		218 (386)	239 (144)	0.009 ∓
Amylase (U/dL)		758 (33)	778 (9)	NS
Urea (mmol/L)		5.340 (2.157)	4.957 (2.040)	NS
Calcium (mmol/L)		0.752 (0.496)	0.401 (0.338)	0.001 ∓
Glucose (mmol/L)		0.174 (0.183)	0.098 (0.115)	0.021 ∓
Quality of life				
OHIP-14		5.2 (4.6)	4.3 (3.4)	NS

SSFR (stimulated salivary flow rate), DMF index (Decayed, Missing and Filled), CPI (Community Periodontal Index), BC (Buffer Capacity)
NS P > 0.05, † Mann-Whitney U Test, ∓ Fisher's Exact Test

Table 2. Bivariate analysis of studied population considering xerostomia as dependent variable

Variables n (%) or mean (SD)	DM1 group with xerostomia n=27	DM1 group without xerostomia n=24	Control group with xerostomia n=8	Control group without xerostomia n=43	P value
Oral health conditions					
DMF index	2.81 (2.98)	4.58 (4.80)	3.13 (3.72)	1.42 (1.74)	NS
CPI		1.63 (1.66)	0.88 (1.81)	0.07 (0.33)	0.000 †
Oral lesions, n (%)	4 (15) 23 (85)	7 (29) 17 (71)	0 (0) 8 (100)	2 (5) 41 (95)	0.046 †
Salivary conditions					
SSFR	1.037 (0.561)	0.885 (0.508)	1.345 (0.528)	1.161 (0.599)	0.043 †
pH	7.9 (0.44)	7,73 (0.61)	7.19 (0.09)	7.45 (0.40)	0.000 †
BC	4.99 (0.81)	4.63 (0.78)	4.20 (1.00)	3.63 (1.09)	0.000 †
Total protein (mg/dL)	164 (99)	139 (82)	201 (206)	239 (130)	0.019 †
Amylase (U/dL)	780 (27)	750 (39)	781 (4)	777 (10)	NS
Urea (mmol/L)	4.967 (2.235)	5.407 (1.738)	4.036 (1.565)	5.085 (2.065)	NS
Calcium (mmol/L)	0.600 (0.431)	0.796 (0.493)	0.313 (0.210)	0.424 (0.361)	0.004 †
Glucose (mmol/L)	0.181 (0.226)	0.144 (0.126)	0.100 (0.128)	0.098 (0.113)	NS
Quality of life					
OHIP-14	7.0 (4.8)	2.8 (2.3)	3.4 (1.7)	4.3 (3.5)	0.002 †

DM1 type 1 diabetes mellitus
SSFR (stimulated salivary flow rate), DMF index (Decayed, Missing and Filled), CPI (Community Periodontal Index), BC (Buffer Capacity)
NS P > 0.05, † Kruskal Wallis Test

Table 3. Multiple logistic regression of the studied population

Dependent variable * [a] Xerostomia 1 (absence=0 e presence=1)						
Independent variable	**B**	**SE**	**Wald**	**P value**	**Exp (B)**	**IC 95%**
DM1	-1.515	0.727	1.000	0.037	0.219	0.062 ; 0.684
Constant	-0.825	5.100		0.872	0.438	
DM1	-1.581	0.613	9.694	0.010	0.206	0.062 ; 0.684
Dependent variable ** [b] OHIP-14 (< 4 points = 0 e ≥ 4 points = 1)						
Independent variables	**B**	**SE**	**Wald**	**P value**	**Exp (B)**	**IC 95%**
DMF index	0.267	0.123	7.000	0.030	1.306	1.021 ; 1.644
Xerostomia	-2.495	0.867	7.921	0.004	0.082	0.018 ; 0.487
Constant	-0.184	14.808	1.000	0.990	0.832	
DMF index	0.259	0.122	8.000	0.033	1.295	1.021 ; 1.644
Xerostomia	-2.367	0.841	8.286	0.005	0.094	0.018 ; 0.487

[a] Variables P > 0.05: SSFR, DMF index, CPI, pH, BC, total proteín, calcium, glucose, and Oral lesions
[b] Variables P > 0.05: SSFR, DMF index, CPI, pH, BC, total proteín, calcium, glucose, and Oral Lesions
CI – Confidence Interval
* n = 102 adolescents
** n = 51 adolescents with type 1 diabetes mellitus (DM1)

8.ARTIGO 5

Condições salivares em adolescentes com *diabetes mellitus* tipo 1

Artigo escrito nas normas da Revista *European Journal of Oral Sciences* disponíveis no site: http://www.wiley.com/bw/submit.asp?ref=0909-8836&site=1

Resumo

Objetivo: Analisar o fluxo salivar e outros fatores salivares em adolescentes com *diabetes mellitus* tipo 1 (DM1). **Design:** Estudo epidemiológico prospectivo com adolescentes (14-19 anos) com DM1 avaliados em dois momemtos: inicial (T0) e 15 meses depois (T1). O controle do diabetes foi determinado pelos testes da hemoglobina glicada (GHb) e glicose capilar (GC), e o tempo de diagnóstico do DM1 foi aferido. A mensuração do fluxo salivar (FSE) foi realizada pela coleta de saliva estimulada. O pH foi avaliado usando pHmetro de bolso e capacidade tampão salivar (CTS) foi determinada por meio da titulometria. Análises das concentrações salivares de proteínas totais, amilase, ureia, cálcio e glicose foram avaliadas usando método colorimétrico. **Resultados:** Um total de 32 adolescentes foram incluídos no estudo. Idade média foi de 17 anos (DP= 1,4). Não houve diferença significativa entre T0 e T1 para os valores médios de GC e GHb. FSE foi de 0,790 mL/min em T0 e 0,881 mL/min em T1 ($P > 0,05$). O pH médio foi 7,5 em T0 e 6,9 em T1 ($P < 0,01$). Valores médios de CTS foram 4,8 e 3,9, em T0 e T1, respectivamente ($P < 0,01$). Hipossalivação foi observada em 16 adolescentes (50%) em T0 e em T1. FSE apresentou correlação positiva com CTS e concentração salivar de amilase, e negativa com ureia e cálcio. **Conclusão:** Adolescentes com DM1 caracterizaram-se por mau controle metabólico (GC e GHb). A hipossalivação em T0 provocou aumento da concentração salivar de ureia e cálcio. Em T1, a hipossalivação provocou diminuição de CTS e concentração salivar de glicose, e aumento de ureia salivar.

Palavras-chaves: diabetes mellitus tipo 1, fluxo salivar, capacidade tampão salivar, saliva, adolescentes, hipossalivação.

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Introdução

A saliva vem sendo utilizada para diagnóstico de afecções dentárias (1), sendo importante para manutenção de um ambiente bucal saudável (2). Muitos fatores podem influenciar na secreção e a na composição salivar, portanto uma padronização para coleta de saliva deve ser realizada (3). Independente da quantidade de saliva variar de pequena a grande, suas várias contribuições para preservação e manutenção da saúde bucal devem ser reconhecidas (1). Análise da saliva é frequentemete usada para diagnóstico de doenças infecciosas e malignas, desordens hereditárias, doenças autoimunes e doenças desordens endócrinas. O diagnóstico pela saliva tem potencialidade no futuro (4).

O *diabetes mellitus* tipo 1 (DM1) é uma disfunção metabólica caracterizada pela hiperglicemia resultante da deficiência definitiva na secreção de insulina, provocada por doença auto-imune e fatores genéticos (5). *American Diabetes Association* (ADA) afirmam que 75% dos casos de DM1 são diagnosticados em pessoas abaixo de 18 anos (6).

A boca é frequentemente exposta a componentes cujos pH diferem do pH normal da saliva (6,5 - 7,5). Estes componentes podem danificar os dentes (erosão) ou as superficies das mucosas (7). A capacidade tampão salivar desempenha um papel importante na manutenção do pH salivar, na remineralização dentária e correlaciona com fluxo salivar (8).

A saliva é composta por uma variedade de eletrólitos e imunoglobulinas: a ureia modula o pH e a capaciade tampão salivar, as proteínas servem para agregar microorganismos bucais, contribuem para metabolismo do biofilme e promovem uma ação antibacteriana, e o cálcio faz antisolubilidade que modula a des-remineralização (1).

O relacionamento entre DM1 e composição salivar tem sido investigada (9 - 15). Alguns estudos transversais têm mostrado que o DM1 provoca alterações bioquímicas na saliva (8 - 13) e uma redução no fluxo salivar (2, 9, 13). No entanto, há carência de estudos longitudinais de pacientes com DM1 para investigação da evolução das alterações salivares provocadas pela doença. O objetivo deste estudo foi analisar prospectivamente o fluxo salivar e outros fatores salivares de adolescentes com DM1.

Materiais e métodos

O presente estudo foi aprovado pelo Comitê de Ética em Pesquisa da Pontifícia Universidade Católica do Paraná e pela Direção do Hospital de Clínicas do Paraná – Universidade Federal do Paraná. Pacientes e responsáveis foram informados sobre o

objetivo e demais aspectos da pesquisa e assinaram o Termo de Consentimento Livre e Esclarecido.

População e design do estudo

O estudo epidemiológico longitudinal foi realizado em duas etapas, inicial (T0) e 15 meses depois (T1). Um total de 32 adolescentes com DM1 (14-19 anos), acompanhados no Ambulatório de Diabetes do Hospital de Clínicas- Universidade Federal do Paraná, foi avaliado em estudo prospectivo no período de 15 meses. A classificação da ADA (5) foi usada para diagnóstico de DM1 e estabelecida como critério de inclusão. Critérios de exclusão foram: presença de condições sistêmicas que pudessem influenciar a fisiologia das glândulas salivares; indivíduos fumantes, etilistas ou usuários de drogas ilícitas.

Avaliação do diabetes mellitus tipo 1

Os resultado dos exames de hemoglobina glicada (GHb), realizados em período inferior a três meses da coleta de saliva, e dos exames de glicose capilar (GC) realizados no momento da coleta de saliva foram registrados. Foram considerados pacientes com bom controle metabólico aqueles que apresentaram valores de GHb ≤ 8,0%, e não-controlados aqueles com valores de GHb > 8,0%. Valores de GC entre 90 a 130 mg/dL caracterizaram bom controle glicêmico (6). O tempo de diagnóstico do DM1 foi verificado.

Coleta e tratamento da saliva

A saliva foi coletada com a utilização de estímulo mastigatório mecânico, por meio de pedaço de látex para garrote estéril de tamanho padronizado (1,5 cm), mastigado continuamente pelo paciente durante 6 minutos. A saliva produzida durante o primeiro minuto de estimulação foi desprezada. Durante os 5 minutos subseqüentes, o paciente expeliu a saliva no interior de um pote coletor universal esterilizado e previamente pesado, numa balança analítica - Marte®, modelo AL 500 (SP – Brasil). A saliva foi coletada no período entre 8:00 horas e 10:00 horas (16).

O fluxo salivar estimulado (FSE) foi avaliado por meio do método gravimétrico, expresso em mL/min. (16) Valores médios de FSE > 0,7 mL/min foram considerados fluxo salivar normal. Valores médios de FSE ≤ 0,7 mL/min forma considerados hipossalivação (7). Imediatamente após coleta da saliva, o pH salivar foi avaliado usando pHmetro de bolso da QUIMIS® Q400BD (eletrodo direto) (Diadema - SP/ Brasil). A capacidade tampão da saliva (CTS) foi determinada por meio da titulometria com 1 mL de saliva adicionado da

3 mL de HCl 5 mmol/L. Após 10 minutos foi verificado o pH final com pHmetro de bolso (17).

Antes de submeter as amostras de saliva às provas bioquímicas, estas foram centrifugadas (3.000 g por 10 min). Concentrações salivares de proteínas totais e cálcio foram determinadas pelo método colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de amilase foi determinada pelo método cinético colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de ureia foi determinada pelo método enzimático colorimétrico (kits LABTEST®/Vista Alegre - MG/ Brasil). Concentração salivar de glicose foi determinada pelo método enzimático colorimétrico (Kits BIOCLIN®/Belo Horizonte - MG/ Brasil). Os testes bioquímicos salivares foram realizados em triplicata.

Variáveis de controle glicêmico e metabólico (GHb e GC), fluxo salivar e os outros fatores salivares foram coletados para os 32 pacientes nos dois momentos: inicial (T0) e após 15 meses (T1).

Análise dos dados

A análise dos dados foi realizada usando o *SPSS versão 15.0 for Windows*. O Teste de Kolmogorov-Smirnov analisou a normalidade das variáveis e o teste de Levene avaliou a homogeneidade de variância. Foram usados os testes t pareado e Mann-Whitney, considerando valores estatísticos significativos ($p \leq 0,05$ e IC 95%). O Teste de Correlação de Pearson foi usado para testar a correlação entre as variáveis do controle metabólico e dos fatores salivares, considerando valores estatísticos signifivativos ($p \leq 0,05$ e IC 95%)

Resultados

Um total de 32 adolescentes foi incluído no estudo. A idade média foi de 17 (DP = 1,4, 14-19), sendo 18 do sexo feminino e 14, do sexo masculino. Tempo médio de diagnóstico do DM1 foi 8,7 anos (DP = 4,8). Média de GC foi 199 mg/dL (DP = 92) em T0 e 160 mg/dL (DP = 74) em T1. Média de GHb foi 9,8 % (DP = 2,4) em T0 e 9,7% (DP = 2,3) em T1. Não houve diferença estatística entre T0 e T1 para GC e GHb (Tabela 1).

Valores médios de FSE foram 0,790 mL/min em T0 e 0,881 mL/min em T1. Não houve diferença estatística entre T0 e T1 para FSE. Os valores médios de pH foram 7,5 (T0) e 6,9 (T1), $P < 0,01$. A CTS média variou de 4,8 em T0 para 3,9 em T1 para adolescentes com DM1, $P < 0,01$ (Tabela 1).

Análise bioquímca da composição salivar realizada em adolescentes com DM1 mostrou que os valores de proteínas totais (P = 0,009) e de glicose (P < 0,01) foram significativamente elevados em T1 comparado com T0. Concentração salivar média de ureia diminui significativamente em T1 comparado com T0 (P = 0,013). Diferenças estatísticas entre T0 e T1 não foram observadas para concentrações salivares de amilase e cálcio (Tabela 1).

Análise bivariada foi aplicada para adolescentes com DM1, considerando FSE > 0,7 mL/min (fluxo normal da saliva) e FSE ≤ 0,7 mL/min (hipossalivação), em T0 e T1. Um total de 16 adolescentes em T0 e T1 teve fluxo normal da saliva e 16 apresentaram hiposalivação nos dois momentos. Em T0, as concentrações salivares de ureia (P = 0,035) e cálcio (P = 0,010) diferiram entre adolescentes com fluxo normal da saliva e aqueles com hipossalivação. Em T1, os valores médios de CTS (P = 0,017), ureia (P = 0,009) e glicose (P = 0,010) apresentaram diferenças significantes entre adolescentes com fluxo normal da saliva e aqueles com hipossalivação (Tabela 2).

Tabela 3 mostra a correlação entre as variáveis do controle metabólico (GC e GHb) e salivares (FSE, CTS, pH, proteínas totais, amilase, ureia, cálcio, glicose) para adolescentes com DM1. GC apresentou correlação positiva com CTS (r = 0,382, $P \leq 0,05$) e ureia (r = 0,452, $P \leq 0,05$) em T0. FSE mostrou correlação positiva com amilase (r = 0,380, $P \leq 0,05$), e negativa com proteínas totais (r = -0,367, $P \leq 0,05$) e cálcio (r = -0,459, $P \leq 0,05$) em T0. Em T1, FSE apresentou correlação positiva com CTS (r = 0,462, $P \leq 0,05$). Deve ser enfatizada a correlação negativa entre FSE e ureia em T0 (r = -0,426, $P \leq 0,05$) e em T1 (r = -0,601, $P \leq 0,01$). Proteínas totais mostraram correlação positiva com ureia em T0 (r = 0,484, $P \leq 0,05$) e em T1 (r = 0,445, $P \leq 0,05$).

Discussão

Neste estudo, adolescentes com DM1 caracterizaram-se por mau controle metabólico mostrado pelos valores médios de GHb e GC nos dois momentos (T0 e T1). A hipossalivação em T0 provocou aumento da concentração salivar de ureia e cálcio. Em T1 a hipossalivação provocou diminuição de CTS e concentração salivar de glicose, e aumento de ureia salivar. A concentração salivar de ureia apresentou correlação positiva com a concentração salivar de proteínas totais e negativa com o FSE em T0 e T1.

O valor médio de FSE de adolescentes com DM1 foi 0,790 mL/min em T0, sem diferença estatística quando comparado ao valor médio de FSE em T1 (0,881 mL/min).

Estes valores médios mostraram que o FSE é baixo em adolescentes com DM1, de acordo com Tenovuo (7). Valores médios de FSE variam de 0,79 mL/min em crianças e adolescentes com DM1 (9) a 1,17 mL/min em adolescentes com DM1 (10), chegando a 2,00 mL/min em crianças e adolescentes com DM1 (11). No presente estudo, hipossalivação foi verificada em 16 adolescentes (50%) com DM1 nos dois momentos (T0 e T1). Houve correlação positiva entre FSE e CTS, e FSE e concentração salivar de amilase. A correlação negativa entre FSE e cálcio pode ser considerado fator protetor à cárie dental (11).

O valor médio de pH salivar nos adolescentes com DM1 (7,5) em T0 foi maior do que em T1 (6,9) (Tabela 1). O valor médio do pH salivar em crianças e adolescentes com DM1 varia de 6,0 (11) a 7,3 (12). Em adolescentes com DM1 foi encontrado valor médio de pH salivar de 7,5 (13). O pH normal da saliva é de 6,5 a 7,5 (7), o que significa que a saliva é ligeiramente ácida. No entanto, o pH salivar varia de acordo com o fluxo salivar podendo ir de 5,3 (baixo fluxo) a 7,8 (fluxo de pico) (1). Neste estudo, o pH pareceu não ser influenciado pela presença de hipossalivação (Tabela 2). Houve correlação negativa entre pH e concentrações salivares de ureia e cálcio em T0 (Tabela 3). Deve-se aprofundar esses achados em outros estudos.

A CTS obteve valores médios de 4,8 (T0) e 3,9 (T1), com diferenças estatísticas entre os dois momentos para adolescentes com DM1. Valores médios de CTS variam de 4,5 (14) em crianças e adolescentes com DM1 a 4,8 (13) em adolescentes com DM1, chegando a 5,4 (15) em adultos jovens com DM1. Krasse (19) aponta que na presença de valores < 4 de CTS, há ineficiência na ação de tamponamento salivar; na presença de valores de CTS que variam entre 4 e 5, há eficiência duvidosa e valores de CTS > 5 são considerados valores normais. No presente estudo, valores médios de CTS apontaram ineficiência na ação de tamponamento salivar em T1 (3,9) e eficiência duvidosa de tamponamento em T0 (4,8). Em T1, houve diferença estatística no valor médio de CTS para os adolescentes com hipossalivação comparados àqueles com FSE normal sendo maior nos últimos. Conforme Wikner & Söder (8), baixo fluxo salivar pode predispor a baixos valores de capacidade tampão.

As concentrações salivares de proteínas totais, ureia e glicose mostraram-se diferentes entre os dois momentos de coleta de saliva (T0 e T1). Valores de proteínas totais entre 109 a 197 mg/dL foram apontados como intervalos de valores normais em FSE

normal (16). No presente estudo, a concentração média de proteínas totais ficou dentro deste intervalo em T0 (181; DP = 147) e maior (320; DP = 263) em T1. Na presença de hipossalivação, os valores elevaram-se nos dois momentos, sem diferença estatística, e ambas as concentrações ficaram acima do normal (16) (Tabela 2). A saliva contém proteínas imunológicas e não imunológicas com propriedades antibacterianas (1). Houve correlação positiva e estatisticamente significativa nos dois momentos entre concentração salivar de proteínas totais e ureia, e entre proteínas totais e cálcio em T0 (Tabela 3).

Valores médios das concentrações de ureia variando de 17 a 41 mg/dL são considerados valores normais na saliva (20). No presente estudo, os valores médios de urea coincidiram com esse intervalo, 34,885 em T0, e 28,130 em T1, sendo significativamante menor em T1. Houve aumento significativo de concentração de ureia salivar na presença de hipossalivação, no entanto as concentrações médias não excederam valores normais (20). A ureia funciona como outro tampão salivar, sendo um componente orgânico que causa rápido aumento no pH do biofilme, por meio da liberação de amônia e dióxido de carbono (21).

Concentrações elevadas de glicose na saliva (>2 mg/dL) em adolescentes com DM1 (20) podem significar evolução da doença durante o acompanhamento e monitoramento da mesma. A glicose salivar possivelmente pode estar relacionada à glicose sanguínea (9, 22, 23). Neste estudo, não houve correlação entre concentração salivar de glicose e o controle glicêmico (GC e GHb). Na presença de hipossalivação, os valores de glicose salivar diminuíram comparados aos valores de glicose em adolescentes com FSE normal, sem diferença estatistica. O tamanho da amostra pode ter influenciado nos resultados.

Neste estudo, as concentrações de cálcio e amilase salivar não apresentraram diferença entre T0 and T1. Valores médios de amilase ficaram altos em relação aos valores apontados por Carda et al (20), que consideraram concentração salivar normal de amilase de 11 a 304 (U/dL). A concentração de amilase salivar diminuiu na hipossalivação enquanto a concentração de cálcio salivar aumentou. Edgar (21) aponta que a concentração normal de cálcio na saliva estimulada é em média 6 mg/dL e sua concentração não é afetada pela dieta. Neste estudo, valores médios de cálcio ficaram abaixo desta média em ambas as etapas da pesquisa, T0 (3,377 mg/dL) e T1 (3,324 mg/dL). O cálcio possui papel fundamental na manutenção da integridade dos dentes pela modulação da remineralização e desmineralização (1).

Uma vez que muitas condições bucais e sistêmicas se manifestam como alterações no fluxo e na composição da saliva, o cirurgião-dentista deve estar atualizado sobre as implicações relacionadas a indivíduos com DM1. Neste estudo, adolescentes com DM1 caracterizaram-se por mau controle metabólico (GC e GHb) e têm dificuldade na manutenção do controle metabólico e glicêmico em adolescentes com DM1 (18).

Há necessidade de outros estudos prospectivos de pacientes com DM1 para investigação da evolução das alterações salivares provocadas pela doença e da correlação com as conseqüências do DM1 na saúde geral. As pesquisa em glândulas salivares devem incluir pesquisas em alterações salivares qualitativas e quantitativas, mecanismos da patofisiologia de glândulas salivares e tratamento de disfunção salivar (24). A evolução do diagnóstico pela saliva é bastante promissora (4).

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TABELAS

Tabela 1. Controle metabólico e fatores salivares da população estudada.

Variáveis média (DP)	T0	T1	Valor P
GC (mg/dL)	199 (92)	160 (74)	NS
GHb (%)	9,8 (2,4)	9,7 (2,3)	NS
FSE (mL/min)	0,790 (0,422)	0,881 (0,457)	NS
pH	7,5 (0,6)	6,9 (0,3)	0,000 ₸
CTS	4,8 (0,8)	3,9 (0,9)	0,000 ₸
Proteínas totais (mg/dL)	181 (147)	320 (263)	0,009 ₸
Amilase (U/dL)	754 (34)	736 (100)	NS
Ureia (mg/dL)	34,885 (12,743)	28,130 (13,281)	0,013 ₸
Cálcio (mg/dL)	3,377 (2,058)	3,324 (2,994)	NS
Glicose (mgl/dL)	4,389 (3,583)	9,519 (4,322)	0,000 ₸

GC (Glicose capilar), GHb (hemoglobina glicada), CTS (capacidade tampão salivar), FSE (Fluxo salivar estimulado), T0 (inicial), T1 (15 meses depois)

₸Teste t pareado, NS (P > 0,05)

Tabela 2. Análise bivariada em adolescentes com *diabetes mellitus* tipo 1, considerando o fluxo salivar estimulado como variável dependente

Variáveis Média (DP)	**T0**			**T1**		
	FSE ≤ 0,7 n = 16	FSE > 0,7 n = 16	**Valor P**	FSE ≤ 0,7 n = 16	FSE > 0,7 n = 16	**Valor P**
pH	7,5 (0,6)	7,5 (0,5)	NS	6,9 (0,4)	7,0 (0,2)	NS
CTS	4,8 (0,7)	4,8 (1,0)	NS	3,5 (0,6)	4,3 (0,9)	0,017₸
Proteínas totais (mg/dL)	218 (197)	145 (54)	NS	377 (316)	262 (191)	NS
Amilase (U/dL)	743 (39)	765 (26)	NS	732 (86)	740 (115)	NS
Ureia (mg/dL)	39,830 (13,237)	29,941 (10,403)	0,035₸	34,181 (3,009)	22,079 (10,825)	0,009₸
Cálcio (mg/dL)	4,326 (2,046)	2,429 (1,629)	0,010₸	3,732 (3,079)	2,916 (2,949)	NS
Glicose (mg/dL)	3,499 (2,510)	5,280 (4,303)	NS	7,696 (3,699)	11,343 (4,222)	0,010₸

CTS (capacidade tampão salivar), FSE (Fluxo salivar estimulado), T0 (inicial), T1 (15 meses depois)
₸ Teste Mann-Whitney U, NS (P > 0,05)

Tabela 3. Teste de Correlação de Pearson entre as variáveis salivares e metabólicas em adolescentes com *diabetes mellitus* tipo 1 em tempo inicial e 15 meses depois.

Variáveis T0 (T1)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. GC	-	-	-	-	-	-	-	-	-
2. GHb	NS	-	-	-	-	-	-	-	-
3. FSE	NS	NS	-	-	-	-	-	-	-
4. pH	NS	NS	NS	-	-	-	-	-	-
5. CTS	0,382 † (0,207)	NS	0,046 (0,462 †)	-0,097 (0,448 †)	-	-	-	-	-
6. Proteínas totais	NS	NS	-0,367 † (-0,303)	-0,253 (0,505 †)	NS	-	-	-	-
7. Amilase	NS	NS	0,380 † (0,072)	NS	0,375 † (0,083)	NS	-	-	-
8. Ureia	0,452 † (0,080)	NS	-0,426 † (-0,601 ₸)	-0,592 ₸ (-0,228)	NS	0,484 † (0,445 †)	NS	-	-
9. Cálcio	NS	NS	-0,469 † (-0,103)	-0,459 † (-0,129)	NS	0,443 † (0,040)	NS	0,676 ₸ (0,077)	-
10. Glicose	NS	NS	NS	NS	NS	NS	NS	-0,136 (0,372 †)	NS

GC (Glicose capilar), GHb (hemoglobina glicada), CTS (capacidade tampão salivar), FSE (Fluxo salivar estimulado), T0 (inicial), T1 (15 meses depois)
₸ P ≤ 0,01, † P ≤ 0,05, NS (P > 0,05)

Salivary status in adolescents with type 1 diabetes mellitus

Objectives: The aim of this study was to analyse salivary flow rate and others salivary factors in adolescents with type 1 diabetes mellitus (DM1). **Design:** A follow-up study was performed in adolescents (14-19 years) with DM1. The subjects were evaluated at a baseline (T0) and after 15 months (T1). Diabetic status was determined by glycosylated hemoglobin (GHb) and capillary glucose (CG) tests, and time of DM1 diagnosis was accounted. Measurement of salivary flow was performed by means of stimulated saliva (SSFR) collection. The pH was determined using a pocket pH meter and buffer capacity (BC) was determined by titration. Analysis of the salivary concentrations of total protein, amylase, urea, calcium and glucose was performed using the colorimetric method. **Results:** A total of 32 subjects was included in the study. Average age was 17 years (SD = 1.4). There were no statistical differences between T0 and T1 for average CG and GHb. SSFR was 0.790 mL/min in T0 and 0.881 mL/min in T1 ($P > 0.05$). The pH means were 7.5 in T0 and 6.9 in T1 ($P = 0.000$). BC at T0 was 4.8, and at T1, it was 3.9 ($P = 0.000$). Hyposalivation was observed in 16 adolescents (50%) at T0 and at T1. SSFR showed a positive correlation with both BC and amylase salivary concentration, and a negative correlation with urea and calcium salivary concentrations. **Conclusions:** Adolescents with DM1 were characterized by poor metabolic control (CG and GHb). Hyposalivation at T0 induced an increase in urea and calcium salivary concentrations. At T1 hyposalivation induced a reduction in BC and in glucose salivary concentration, and an increase in urea salivary concentration.

Key words: type 1 diabetes mellitus, flow rate, buffer capacity, saliva, adolescents, hyposalivation.

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Introduction

Saliva has been used to aid in the diagnosis of dental disease (1), and it is important in maintaining a healthy oral environment (2). Several factors can influence salivary secretion and composition, thus a precise standard for saliva collection must be established (3). Whether saliva occurs in quantities large or small, recognition should be given to the many contributions it makes to the preservation and maintenance of oral systemic health (1). Saliva analysis is currently used for diagnosis of infectious and malignant diseases, hereditary disorders, autoimmune diseases, and endocrine disorders. Salivary diagnostics has a potential future (4).

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 (5). The American Diabetes Association (ADA) reports that 75% of DM1 cases are diagnosed in persons under age 18 (6).

The human mouth is quite frequently exposed to components whose pH differs from the normal pH of saliva (6.5-7.5). These components may cause damage to teeth (erosion) or oral mucosa surfaces (7). The buffer capacity of saliva plays a role in the maintenance of salivary pH, in dental remineralization and correlates with salivary flow rate (8). Saliva is composed of a variety of electrolytes and immunoglobulins: urea acts modulating pH and buffering capacity of saliva; protein serves to cleanse, aggregate, and/or attach oral microorganisms, contributes to dental plaque metabolism, and provides antibacterial action; and calcium is an antisolubility factor that modulates demineralization and remineralization (1).

The relationship between DM1 and salivary composition has been investigated (9 - 15). Some cross-sectional studies have shown that DM1 results in biochemical alterations to saliva (8-13) and a reduction in salivary flow (2, 9, 13). Moreover, there are limited studies involving the follow-up of patients with DM1 to investigate the evolution os salivary alterations caused by the disease. Thus, the aim of this study was to prospectively analyse salivary flow rate and others salivary factors in adolescents with DM1.

Material 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.

Study groups and study design

This longitudinal epidemiological study was assessed at a baseline (T0) and after 15 months (T1). A total of 32 adolescents with DM1 (14-19 years), who attend the Diabetes Outpatients Department of the Paraná Federal University Teaching Hospital, was invited to participate in this 15-month prospective study. The diagnosis of DM1 using the ADA (5) classification was established as a criterion for inclusion. The exclusion criteria used for the sample were: presence of systemic conditions that could influence the salivary gland physiology, psychotropic drugs users, smokers or illicit drugs users and alcohol users.

Evaluation of type 1 diabetes mellitus

The results of glycosylated hemoglobin (GHb) tests performed less than three months prior to saliva collection and the results of capillary glucose (CG) tests performed at the time of saliva collection were recorded. Patients with good metabolic control were considered to be those with GHb values of ≤ 8.0 %, whereas poorly-controlled patients were considered to be those with GHb values of > 8.0 %. CG values between 90 and 130 mg/dL characterized good glycemic control (6). Time of diagnosis of DM1 was accounted.

Collection and treatment of saliva

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. (16)

Stimulated saliva flow rate (SSFR) was evaluated by means of the gravimetric method and expressed in mL/min. SSFR values of > 0.7 mL/min were considered to represent normal saliva flow. SSFR values of ≤ 0.7 mL/min were considered to indicate hyposalivation (7). The pH value was determined using a QUIMIS® Q400BD (direct electrode) pocket pH meter (Diadema-SP/Brazil). Buffer capacity (BC) was determined by titration with 3 mL of HCl 5 mmol/L added to 1 mL of saliva. After 10 minutes the final pH value was measured using a pocket pH meter (17).

The remaining saliva samples were centrifuged (3.000 g for 10 min). Total protein and calcium concentrations were determined by the colorimetric method (LABTEST® kits/Vista Alegre - MG/ Brazil). Amylase concentrations were determined by the kinetic colorimetric method (LABTEST® kits/Vista Alegre - MG/ Brazil). Urea concentrations were determined by the enzymic colorimetric method (LABTEST® kits/Vista Alegre - MG/ Brazil). Glucose was analysed by an enzymic colorimetric method (BIOCLIN® kit/Belo Horizonte - MG/ Brazil). The determination of the salivary concentrations was performed three times.

Metabolic and glycemic control variables (GHb and CG), and salivary flow and others factors were assessed from the 32 patients in two moments: at a baseline (T0) and after 15 months (T1).

Statistical analysis

The data was 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 the paired t-test and the Mann-Whitney test considering statistically significant values ($p \leq 0.05$ and CI 95%). The Pearson correlation test was performed between the metabolic control variables and the salivary factors variables, considering statistically significant values ($p \leq 0.05$ and CI 95%).

Results

A total of 32 subjects was included in the study. Average age was 17 years (SD = 1.4, 14-19), 18 were women and 14 were men. Time of diagnosis of DM1 was 8.7 years (SD = 4.8). Average CG was 199 mg/dL (SD = 92) at T0 and 160 mg/dL (SD = 74) at T1. Average GHb was 9.8 % (SD = 2.4) at T0 and 9.7% (SD = 2.3) at T1. There were no significant differences between T0 and T1 for CG and GHb (Table 1).

SSFR mean value was 0.790 mL/min at T0 and 0.881 mL/min at T1. There was no statistically significant difference between T0 and T1 for SSFR. The pH mean values were 7.5 (T0) and 6.9 (T1), $P = 0.000$. The BC mean values varied from 4.8 at T0 to 3.9 at T1 in adolescents with DM1, $P = 0.000$ (Table 1).

Analysis of the biochemical composition of saliva showed that the adolescents with DM1 had significantly higher values of total protein ($P = 0.009$) and glucose ($P = 0.000$) at T1 when compared with T0. Urea concentration mean value had a significant decrease at T1 compared with T0 ($P = 0.013$). No significant differences between T0 and T1 in

adolescents with DM1 were found for amylase and calcium salivary concentrations (Table 1).

Bivariate analysis was performed considering SSFR values of > 0.7 mL/min (normal saliva flow) and SSFR values of ≤ 0.7 mL/min (hyposalivation) at T0 and T1 in adolescents with DM1. A total of 16 adolescents at T0 and at T1 had normal saliva flow and 16 had hyposalivation in both moments. At T0, both urea (P = 0.035) and calcium (P = 0.010) salivary concentrations were different between adolescents with normal saliva flow and those with hyposalivation. At T1, BC (P = 0.017), urea (P = 0.009) and glucose (P = 0.010) mean values differed between adolescents with normal saliva flow and those with hyposalivation (Table 2).

Table 3 shows the correlation between the metabolic (CG and GHb) and the salivary (SSFR, BC, pH, total protein, amylase, urea, calcium, glucose) variables in adolescents with DM1. CG showed positive correlation with BC (r = 0.382, $P \leq 0.05$) and urea (r = 0.452, $P \leq 0.05$) at T0. SSFR showed positive correlation with amylase (r = 0.380, $P \leq 0.05$), and negative correlation with total protein (r = -0.367, $P \leq 0.05$) and calcium (r = -0.459, $P \leq 0.05$) at T0. At T1, SSFR values had a positive correlation with BC (r = 0.462, $P \leq 0.05$). The negative correlation between SSFR and urea at T0 (r = -0.426, $P \leq 0.05$) and at T1 (r = -0.601, $P \leq 0.01$) should be emphasized. Total protein showed positive correlation with urea at T0 (r = 0.484, $P \leq 0.05$) and at T1 (r = 0.445, $P \leq 0.05$).

Discussion

In this study, adolescents with DM1 were characterized by poor metabolic control demonstrated by the mean GHb and CG values at both times of measurement (T0 and T1). Hyposalivation at T0 induced an increase in the salivary concentration of urea and calcium. At T1 hyposalivation induced a reduction in BC mean values and in glucose salivary concentration, and an increase in salivary urea concentration. The salivary concentration of urea presented a positive correlation with total protein salivary concentration and a negative correlation with SSFR at both T0 and T1.

SSFR mean values in adolescents with DM1 were 0.790 mL/min at T0 and 0.881 mL/min at T1, with no statistical difference between the moments. These SSFR mean values showed to be low in adolescents with DM1, according to Tenovuo (7). SSFR mean values vary from 0.79 mL/min in children and adolescents with DM1 (9) to 1.17 mL/min in adolescents with DM1 (10), reaching 2.00 mL/min in children and adolescents with DM1

(11). In the present study, hyposalivation was detected in 16 adolescents (50%) with DM1 at both moments (T0 and T1). Furthermore, there was a positive correlation between SSFR and both BC and amylase salivary concentration. The negative correlation between SSFR and calcium may be a protective factor against dental caries (11).

Salivary pH mean values in the adolescents with DM1 (7.5) at T0 was higher than the mean values at T1 (6.9) (Table 1). The mean salivary pH value in children and adolescents with DM1 varies from 6.0 (11) to 7.3 (12). Mean salivary pH of 7.5 has been found in adolescents with DM1 (13). Normal saliva pH is between 6.5 and 7.5 (7), which means that saliva is slightly acid. However, salivary pH varies with salivary flow and can range between 5.3 (low flow) and 7.8 (peak flow) (1). In this study pH did not appear to be influenced by the presence of hyposalivation (Table 2). There was a negative correlation between pH and urea, and pH and calcium salivary concentrations at baseline (Table 3). These findings need to be examined in further studies.

The mean BC values were 4.8 (T0) and 3.9 (T1), with statistical differences between both moments for adolescents with DM1. BC mean values vary from 4.5 (14) in children and adolescents with DM1 to 4.8 (13) in adolescents with DM1, reaching 5.4 (15) in young adults with DM1. Krasse (19) indicates that in the presence of BC values of < 4 there is inefficiency in salivary buffering action; efficiency is doubtful in the presence of BC values varying between 4 and 5 and BC values of > 5 are considered to be normal. In the present study, BC mean values indicated inefficiency in salivary buffering action at T1 (3.9) and doubtful buffering efficiency at T0 (4.8). At T1 there was a statistical difference between the mean BC value in adolescents with hyposalivation compared with that with normal SSFR, being higher in the latter. According to Wikner, Söder (8), a low flow rate may predict a low buffer value.

Total protein, urea and glucose salivary concentrations were different at the two saliva collection times (T0 and T1). Total protein values between 109 and 197 mg/dL have been indicated as normal interval values in normal SSFR (16). In the present study, the mean concentration of total protein was within this interval at T0 (181, SD = 147) and above it (320, SD = 263) at T1. In the presence of hyposalivation the values were higher at both times of measurement, without statistical difference, and both concentrations were above normal values (16) (Table 2). Saliva contains immunological and non-immunological proteins with antibacterial properties (1). At both times of measurement there was a positive

and significant correlation between the salivary concentration of total protein and urea, and also between salivary total protein and calcium (Table 3).

Urea concentrations varying between 17 and 41 mg/dL in saliva are considered to be normal (20). In the present study, the mean urea values coincided with this interval, being 34.885 (SD = 12.743) at T0, and 28.130 (SD = 13.281) at T1, being significantly lower at T1. There was a significant increase in salivary urea concentration in the presence of hyposalivation at both moments (T0 and T1), although the mean concentrations did not exceed normal values (20). Urea functions as another salivary buffer, being an organic component that causes a rapid biofilm pH increase, by releasing ammonia and carbon dioxide (21).

High glucose concentrations in saliva (> 2 mg/dL) in adolescents with DM1 (20) may show the evolution of this disease during its follow-up and monitoring. Salivary glucose may possibly be related to blood glucose (9, 22, 23). In this study there was no correlation between salivary glucose concentration and metabolic control (CG and GHb). Salivary glucose values decreased in the presence of hyposalivation compared with glucose values in adolescents with normal SSFR, without statistical difference. The size of the sample may have influenced the results.

In this study, there were no statistical difference for salivary calcium and amylase concentrations at T0 and T1. The mean amylase values were higher than the values reported by Carda et al (20), who considered normal salivary amylase concentration to be between 11 and 304 (U/dL). Salivary amylase concentration decreased during hyposalivation whereas the concentration of salivary calcium increased. Edgar (21) indicates that normal calcium concentration in saliva is 6 mg/dL on average and that its concentration is not affected by diet. In this study the mean calcium values were below this average at both times of measurement, T0 (3.377 mg/dL) and T1 (3.324 mg/dL). Calcium plays a fundamental role in maintaining the integrity of the teeth by modulating remineralization and demineralization (1).

Since many oral and systemic conditions manifest themselves as changes in the flow and composition of saliva the dental practitioner is advised to remain up-to-date (3) with the current literature on subjects with DM1. In this study, adolescents with DM1 were characterized by poor metabolic control (CG and GHb) and adolescents with DM1 have had difficulty in maintaining metabolic and glycemic control (18).

Further studies are needed involving the follow-up of patients with DM1 to investigate the evolution of salivary alterations induced by the disease and the correlation with the consequences of DM1 on overall health. Salivary gland research should include research on salivary qualitative and quantitative changes, mechanisms of salivary gland pathophysiology, and management of salivary dysfunction (24). The evolution of salivary diagnostics has much promise, and is bound to be widespread in the not too distant future (4).

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Tables

Table 1. Metabolic control and salivary factors of the studied population.

Variables mean (SD)	T0	T1	P value
CG (mg/dL)	199 (92)	160 (74)	NS
GHb (%)	9.8 (2.4)	9.7 (2.3)	NS
SSFR (mL/min)	0.790 (0.422)	0.881 (0.457)	NS
pH	7.5 (0.6)	6.9 (0.3)	0.000 ₸
BC	4.8 (0.8)	3.9 (0.9)	0.000 ₸
Total Protein (mg/dL)	181 (147)	320 (263)	0.009 ₸
Amylase (U/dL)	754 (34)	736 (100)	NS
Urea (mg/dL)	34.885 (12.743)	28.130 (13.281)	0.013 ₸
Calcium (mg/dL)	3.377 (2,058)	3.324 (2.994)	NS
Glucose (mg/dL)	4.389 (3.583)	9.519 (4.322)	0.000 ₸

CG (Capillary glucose), GHb (Glycosylated hemoglobin), BC (buffer capacity), SSFR (stimulated salivary flow rate), T0 (baseline), T1 (15 months follow-up)
₸ paired t test, NS ($P > 0.05$)

Table 2. Bivariate analysis of the stimulated salivary flow rate in adolescents with type 1 diabetes mellitus

Variables Mean (SD)	T0			T1		
	SSFR ≤ 0.7 n = 16	SSFR > 0.7 n = 16	**P value**	SSFR ≤ 0.7 n = 16	SSFR > 0.7 n = 16	**P value**
pH	7.5 (0.6)	7.5 (0.5)	NS	6.9 (0.4)	7.0 (0.2)	NS
BC	4.8 (0.7)	4.8 (1.0)	NS	3.5 (0.6)	4.3 (0.9)	0.017Ŧ
Total Protein (mg/dL)	218 (197)	145 (54)	NS	377 (316)	262 (191)	NS
Amylase (U/dL)	743 (39)	765 (26)	NS	732 (86)	740 (115)	NS
Urea (mg/dL)	39.830 (13.237)	29.941 (10.403)	0.035Ŧ	34.181 (3.009)	22.079 (10.825)	0.009Ŧ
Calcium (mg/dL)	4.326 (2.046)	2.429 (1.629)	0.010Ŧ	3.732 (3.079)	2.916 (2.949)	NS
Glucose (mg/dL)	3.499 (2.510)	5.280 (4.303)	NS	7.696 (3.699)	11.343 (4.222)	0.010Ŧ

SSFR (stimulated salivary flow rate), BC (buffer capacity), T0 (baseline), T1 (15 months follow-up)
Ŧ Mann-Whitney U test, NS (P > 0.05)

Table 3. Pearson Correlation test between metabolic and salivary variables in adolescents with type 1 diabetes at baseline and after 15 months.

Variables T0 (T1)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. CG	-	-	-	-	-	-	-	-	-
2. GHb	NS	-	-	-	-	-	-	-	-
3. SSFR	NS	NS	-	-	-	-	-	-	-
4. pH	NS	NS	NS	-	-	-	-	-	-
5. BC	0.382 † (0.207)	NS	0.046 (0.462 †)	-0.097 (0.448 †)	-	-	-	-	-
6. Total Protein	NS	NS	-0.367 † (-0.303)	-0.253 (0.505 †)	NS	-	-	-	-
7. Amylase	NS	NS	0.380 † (0.072)	NS	0.375 † (0.083)	NS	-	-	-
8. Urea	0.452 † (0.080)	NS	-0.426 † (-0.601 Ŧ)	-0.592 Ŧ (-0.228)	NS	0.484 † (0.445 †)	NS	-	-
9. Calcium	NS	NS	-0.469 † (-0.103)	-0.459 † (-0.129)	NS	0.443 † (0.040)	NS	0.676 Ŧ (0.077)	-
10. Glucose	NS	NS	NS	NS	NS	NS	NS	-0.136 (0.372 †)	NS

CG (capillary glucose), GHb (glycosylated hemoglobin), SSFR (stimulated salivary flow rate), BC (buffer capacity)
T0 (baseline), T1 (15 months follow-up)
Ŧ P ≤ 0.01, † P ≤ 0.05, NS (P > 0.05)

9.CONCLUSÃO

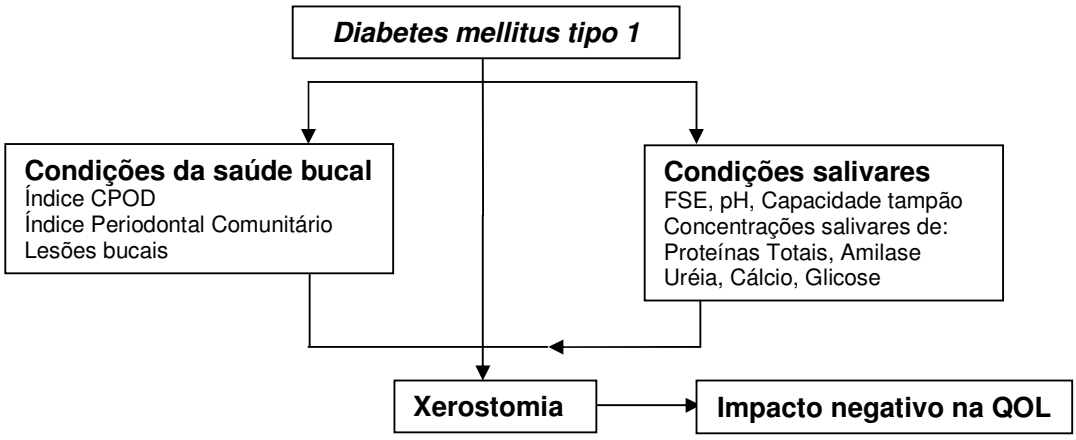
O Artigo 1, "*Impact of xerostomia on the quality of life of adolescents with type 1 diabetes mellitus"*, avaliou o impacto da xerostomia na qualidade de vida de adolescentes com DM1. A xerostomia mostrou-se prevalente entre adolescentes com DM1 e provocou impacto negativo na QOL, especialmente nas seguintes dimensões: limitação funcional, incapacidade física, incapacidade psicológica, incapacidade e desvantagem social.

"*Association between metabolic control and oral health in adolescents with type 1 diabetes mellitus",* artigo 2, avaliou a relação entre o controle metabólico e a saúde bucal de adolescentes com DM1. O DM1 e o mau controle metabólico em adolescentes pareceram diminuir o FSE, aumentar a prevalência de lesões da mucosa oral, e a prevalência da doença periodontal. O DM1 em adolescentes, independente do controle metabólico, aumentou a experiência de cárie.

O artigo 3, "Impacto da hiperglicemia na composição e fluxo salivar e na xerostomia de adolescentes com *diabetes mellitus* tipo 1", avaliou a hiperglicemia na composição salivar e xerostomia em adolescentes com DM1. Como conclusão, a hiperglicemia mostrou-se fator de risco para diminuição do FSE, aumento de concentrações salivares de cálcio e ureia em adolescentes com DM1.

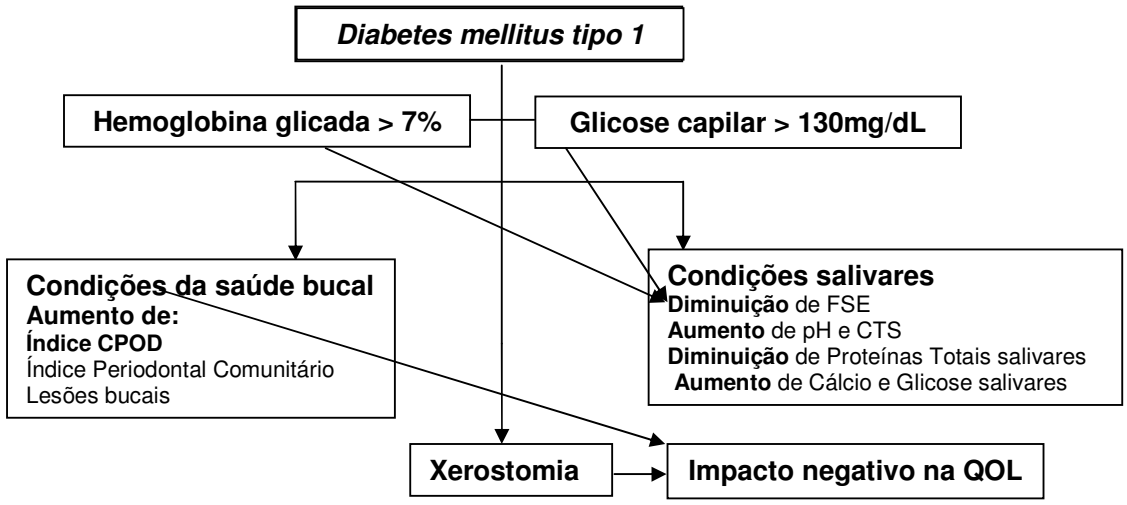
"Xerostomia e qualidade de vida: condições de saúde bucal e salivares em adolescentes com *diabetes mellitus* tipo 1", artigo 4, investigou a influência das condições de saúde bucal e salivares na prevalência da xerostomia e seu impacto na qualidade de vida (QOL) de adolescentes com DM1, Figura 1. Na análise bivariada, o DM1 mostrou influenciar na maior prevalência de xerostomia e não ter impacto negativo na QOL de adolescentes comparado com adolescentes sem diabetes. A presença de DM1 foi significativa para a piora das condições de saúde bucal e nas alterações das condições salivares. Experiência de cárie e concentrações salivares de amilase, ureia e glicose não se mostraram associadas à xerostomia. O DM1 mostrou provocar xerostomia. Por outro lado, a xerostomia e a experiência de cárie mostraram associação com a QOL. A Figura 2 mostra os efeitos do DM1 na saúde bucal de adolescentes e o modelo da determinação da xerostomia e o impacto na QOL com a análise da regressão logística.

Figura 1. Modelo teórico de determinação da xerostomia e impacto negativo na QOL.



"Condições salivares em adolescentes com *diabetes mellitus* tipo 1", artigo 5. Objetivou analisar as características salivares em adolescentes com DM1 em estudo epidemiológico de follow-up com 32 adolescentes com DM1 avaliados em dois momentos, inicial e 15 meses depois. Neste estudo, adolescentes com DM1 caracterizaram-se por mau controle metabólico e glicêmico mostrado pelos valores médios de hemoglobina glicada e glicose capilar nos dois momentos. A hipossalivação provocou aumento da concentração salivar de ureia nos dois momentos. A concentração salivar de ureia apresentou correlação positiva com a concentração de proteínas totais e negativa com o fluxo salivar estimulado nos dois momentos.

Figura 2. Efeitos do DM1 na saúde bucal de adolescentes e modelo teórico de determinação da xerostomia e o impacto negativo na QOL.



ANEXO 1

Pontifícia Universidade Católica do Paraná
Pró-Reitoria Acadêmica e de Pesquisa
Diretoria de Pesquisa e Programas Stricto Sensu

Curitiba, 15 de fevereiro de 2007.
Of. 013/07/CEP-PUCPR

Ref. "**Efeitos do diabetes mellitus na saúde bucal de adolescentes com idade de 12 a 19 anos**"

Prezado (a) Pesquisador (es),

Venho por meio deste informar a Vossa Senhoria que o Comitê de Ética em Pesquisa da PUCPR, no **dia 14 de fevereiro** do corrente ano aprovou o Projeto Intitulado "**Efeitos do diabetes mellitus na saúde bucal de adolescentes com idade de 12 a 19 anos**", pertencente ao Grupo III, sob o registro no **CEP nº 1546,** e será encaminhado a CONEP para o devido cadastro. Lembro ao senhor (a) pesquisador (a) que é obrigatório encaminhar relatório anual parcial e relatório final a este CEP.

Atenciosamente,

Prof.Sergio Surugi de Siqueira
Coordenador do Comitê de Ética em Pesquisa - PUCPR

Ilma Sra
Ivana Maria Saes Bussato

Rua Imaculada Conceição, 1155 Prado Velho CEP 80215 901 Curitiba Paraná Brasil
Caixa Postal 17315 CEP 80242 980 Tel.: (41) 3271 1543 Tel./Fax: (41) 3271 1335 www.pucpr.br

HOSPITAL DE CLÍNICAS
UNIVERSIDADE FEDERAL DO PARANÁ

DECLARAÇÃO

Declaramos para devidos fins que o Hospital de Clínicas da Universidade Federal do Paraná está ciente e concorda com a realização do Projeto de pesquisa clínica intitulado "**Efeitos do diabetes mellitus na saúde bucal de adolescentes com idade de 12 a 19 anos**", tendo como pesquisador Ivana Maria Saes Busato.

O estudo será realizado junto ao Ambulatório de Endocrinologia deste Hospital, sem ônus ambulatoriais para esta Instituição e com consentimento do Responsável pelo citado ambulatório, Dra. Rosangela R. Réa.

Curitiba, 12 de março de 2007.

Profa. Dra. Heda Maria B. dos S. Amarante
Diretora de Corpo Clínico
Hospital de Clínicas da UFPR

rua General Carneiro 181 - CEP 80060-900 - Fone (041) 362-2028 - FAX (041)264-5872 - Ctba-PR

ANEXO 3

Forwarded message from CNPq <dpt@cnpq.br> -----

Date: Wed, 19 Dec 2007 10:32:53 -0200 (BRST)

From: CNPq <dpt@cnpq.br>

Reply-To: CNPq <dpt@cnpq.br>

Subject: CNPq - Resultado do julgamento - [477932/2007-0] - Edital MCT/CNPq 15/2007 - Universal - Faixa A - Até R$ 20.000,00

To: luciana.alanis@pq.cnpq.br

Nome: Luciana Reis Azevedo Alanis

Processo: 477932/2007-0

Projeto:Efeitos do diabetes mellitus na saúde bucal em adolescentes com idade de 12 a 19 anos

Prezado (a) Senhor(a),

Comunicamos que, com base na recomendação do Comitê Odontologia e de acordo com o que estabelece o Edital MCT/CNPq 15/2007 - Universal - Faixa A - Até R$ 20.000,00, a Diretoria do CNPq aprovou a concessão para o desenvolvimento do seu projeto.

Para a implementação do benefício é necessário preencher o Termo de Concessão e Aceitação que se encontra na página do CNPq, no endereço http://efomento.cnpq.br/efomento/termo?token=evG55708P088210182056071821718 8 e enviá-lo eletronicamente com a MÁXIMA BREVIDADE, clicando no botão "Enviar ao CNPq". Informamos, ainda, que está seguindo pelos Correios Carta de Autorização de Abertura de Conta Tipo B junto ao Banco do Brasil S/A, em face das dificuldades operacionais do Banco em adotar modelo em formato eletrônico.

Atenciosamente,

Jose Oswaldo de Siqueira

Diretor de Programas Tematicos e Setoriais

ANEXO 4

XEROSTOMIA – ÚLTIMOS 6 MESES

A - Você tem sensação de "boca seca"? 1 sim ☐ 2 não ☐

B – Como você descreve a quantidade de saliva na sua boca? 1 baixa ☐ 2 normal ☐

C - Você tem dificuldade para engolir a comida? 1 sim ☐ 2 não ☐

D - Você precisa de uma bebida para engolir as refeições? 1 sim ☐ 2 não ☐

OHIP14: ÚLTIMOS 06 MESES	**PESO**
Você teve problemas para falar alguma palavra?	**0,51**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você sentiu que o sabor dos alimentos tem piorado?	**0,49**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você sentiu dores em sua boca ou nos seus dentes?	**0,34**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você se sentiu incomodado(a) ao comer algum alimento?	**0,66**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você ficou preocupado(a)?	**0,45**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você se sentiu estressado(a)?	**0,55**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Sua alimentação ficou prejudicada?	**0,52**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você teve que parar suas refeições?	**0,48**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você encontrou dificuldade para relaxar?	**0,60**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você se sentiu envergonhado(a)?	**0,40**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você ficou irritado(a) com outras pessoas?	**0,62**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você teve dificuldades para realizar suas atividades diárias?	**0,38**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você sentiu que a vida, em geral, ficou pior?	**0,59**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	
Você ficou totalmente incapaz de fazer suas atividades diárias?	**0,41**
0. ☐ nunca 1. ☐ raramente 2. ☐ às vezes 3. ☐ repetidamente 4.☐ sempre	

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