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By Alejandra Saldivar-De la Torre, Miranda Rodríguez-Gardea, Rosaura Pacheco-Santiesteban, Martín Cisneros-Castolo, Karla Elena Martínez-Aguilar, César Pacheco-Tena, Francisco Javier Zavala-Díaz de la Serna & Víctor Adolfo Ríos-Barrera

Autonomous University of Chihuahua

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ORAL LESIONS IN PEDIATRIC PATIENTS IN NORTH MEXICO WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA OR TYPE 1 DIABETES MELLITUS AS UNDERLYING DISEASE

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Oral Lesions in Pediatric Patients in North Mexico with B-Cell Acute Lymphoblastic Leukemia or Type 1 Diabetes Mellitus as Underlying Disease

Alejandra Saldivar-De la Torre ^α, Miranda Rodríguez-Gardea ^σ, Rosaura Pacheco-Santiesteban ^ρ,
Martín Cisneros-Castolo ^ω, Karla Elena Martínez-Aguilar [¥], César Pacheco-Tena [§],
Francisco Javier Zavala-Díaz de la Serna ^χ & Víctor Adolfo Ríos-Barrera ^ν

Abstract- Oral involvement in the pediatric age does not occur as an isolated event, frequently involves a systemic disease being Leukemias -especially B-cell Acute Lymphoblastic Leukemia (B-cell ALL)- and Type 1 Diabetes Mellitus (T1DM) the most relevant.

Objective: To find which oral manifestations are observed with greater more frequently in pediatric patients with B-cell ALL or T1DM and to relate these findings with their pathophysiology.

Methodology: We formed three study groups, with five patients each: 1) children with T1DM, 2) infants with B-cell ALL, and 3) healthy children. The age range was five to fifteen years. Data were collected from: 1) clinical examination, 2) interrogation of parents or guardians, and 3) review of the clinical record, and 4) Blood count (BC). We utilized Silness and Loe gingival index (GI) to quantify the on dental-bacterial plaque (DBP) to measure soft-tissues' risk affection because of bad oral hygiene. We employed CPOD-ceod index (referring to caries, missing or obturated teeth) to measure the cariogenic risk in dental organs. Blood count (BC) was utilized to find out blood alterations consistent with clinical findings.

Results: 60% had xerostomia and 80% of the patients had different soft tissue lesions. Children with T1DM presented gingivitis (40%) and traumatic ulcers (40%). In cases with B-cell ALL, lesions were more varied: gingivitis (20%), traumatic ulcers (20%), herpetiform ulcers (20%) -an accumulated of 40% of ulcers-, candidiasis (40%), and mucositis (20%). The lowest GI and CPOD-ceod indices were found in the T1DM group (2.2 and 1.0, respectively); in healthy children, their values were common (2.7 and 3.2, respectively), and in the B-cell ALLset had the highest values (4.6 and 5.2, respectively). BC were normal in T1DM and healthy groups whereas the B-cell ALL group evidenced neutropenia, lymphopenia, and megaloblastic anemia.

Conclusions: T1DM and B-cell ALL affect homeostasis of the oral cavity, which predisposes to lesions formation. In B-cell ALL cases, the processes are more related to immunosuppression while in cases with T1DM they are more related to physicochemical and metabolic alterations. Treatments of underlying nosological entities also influences the oral lesions formation, specifically, mucositis in B-cell ALL, and gingival alterations in T1DM.

Keywords: oral lesions, underlying disease, Type 1 Diabetes Mellitus, B-cell Acute Lymphoblastic Leukemia, immunocompromise, metabolic disbalance, oral altered homeostasis.

Author α: Department of Pediatric Stomatology. Faculty of Dentistry. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico.
Medical-Stomatological Research Laboratory. Faculty of Dentistry. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico.
e-mail: dra.saldivar-delatorre@gmail.com

Author σ: Medical-Stomatological Research Laboratory. Faculty of Dentistry. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico. e-mail: mirandar_82@hotmail.com

Author ρ: Department of Pediatric Stomatology. Faculty of Dentistry. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico.
e-mail: rpacheco@uach.mx

Author ω: Faculty of Medicine and Biomedical Sciences. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico.
e-mail: mcisneros@uach.mx

Author ¥: Children's Specialty Hospital of Chihuahua. Chihuahua, Chih. Mexico. e-mail: kema1310@hotmail.com

Author §: Faculty of Medicine and Biomedical Sciences. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico.
e-mail: dr.pachecotena@gmail.com

Author χ: Faculty of Chemical Sciences. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico. e-mail: fzavala@uach.mx

Corresponding Author ν: Medical-Stomatological Research Laboratory. Faculty of Dentistry. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico.

Department of Pediatric Stomatology. Faculty of Dentistry. Autonomous University of Chihuahua. Chihuahua, Chih. Mexico.
e-mails: victoradolfo.rb@gmail.com, varios@uach.mx

1. INTRODUCTION

Oral condition in pediatric age constitutes a public health problem, reaching a prevalence of 28.9% (1). Caries is the most frequent ailment, and its origin is multifactorial. However, some reports in the literature show also other significant to matological alterations associated with an underlying systemic disease (2, 3). Some of the most prevalent systemic diseases observed in pediatric patients are Leukemia (4) and Diabetes Mellitus (3). Leukemias are malignant neoplasms of the bone marrow, with a rate of 13 cases per 100,000 inhabitants, with a slight predominance in the male gender (4) Based on the American Cancer Society classification, B-cell Acute Lymphoblastic Leukemia (B-cell ALL) is the most common in this population (80%) (4, 5) In United States of America, the incidence of B-cell ALL is about 1.6 per 100,000 population (5) In Mexico, leukemias are among the top 3 causes of mortality in children in the 1 to 14 years range.

In the Mexican State of Chihuahua, leukemias occupy the fifth and second places of mortality in the age groups of one to four years and five to fourteen years, respectively (6). In addition to the clinical picture of systemic manifestations (fever, anemia, bone pain, asthenia, adynamia, ecchymosis, bleeding, adenomegaly, and hepatosplenomegaly) various oral lesions are also frequently observed, mainly: ulcers, xerostomia, gingivitis, and mucositis (4, 7) plus added infections, particularly *Candida albicans*. Regarding Diabetes Mellitus, between 87% and 91% of people suffer from Type 2 Diabetes Mellitus whereas 7% to 12% are affected by Type 1 Diabetes Mellitus (T1DM), and 1% to 3% corresponds to other variants (8). Of the population of patients with T1DM, the vast majority start at an early age, being currently the most frequent autoimmune disease in childhood (9). Besides the long-term complications (nephropathy, heart disease, diabetic foot, retinopathy, cerebral vascular events, etc.), oral lesions have been seen very frequently; especially those related to periodontal disease: erythema, gingivitis, ulcers, bleeding (10), xerostomia, and caries (11).

This work studied pediatric patients with B-cell ALL or T1DM as an underlying systemic disease; purposes were to find which oral lesions are observed more frequently and find out a relation between these findings with the pathophysiology of the underlying disease.

II. METHODOLOGY

The authorization corresponded to the Bioethics Department of the Autonomous University of Chihuahua (UACH; from Spanish: Universidad Autónoma de Chihuahua) and the Children's Hospital of Specialties of Chihuahua (HIECH; from Spanish: Hospital Infantil de Especialidades de Chihuahua).

a) Data collection

Parents or guardian's participant signed the informed consent letter to take part in the research project. Likewise, each participant was notified about the study and signed the informed letter of consent, according to the criteria set out in the Official Mexican Standard NOM-012-SSA3-2012 and the Regulations of the General Health Law on Health Research.

b) Study groups

This study included fifteen patients, with whom we formed three groups:

- 1) T1DM patients
- 2) B-cell ALL
- 3) Healthy children

Each group consisted of five children, and they were paired by age and sex with children in the other groups (Table S1).

Patients' data were obtained from the file and by direct interrogation to parents, guardians, and patients. We perform a clinical examination with emphasis on the oral cavity. Finally, were analyzed blood count reports.

A pediatric oncologist and pediatric endocrinologist reported diagnosis and managed treatments. All individuals met the inclusion and exclusion criteria (Appendix S1):

- 1) T1DM. All of them with insulin treatment.
- 2) B-cell ALL. They were in the first week of the induction to remission phase of chemotherapy, based on Saint Jude 16 protocol (12, 13); briefly, children received: prednisone, daunorubicin, vincristine, L-asparagine, etoposide, and triple intrathecal therapy during this stage.
- 3) Healthy children. They were obtained from patients who enter for light medical procedures (for example, minor trauma treatments).

c) Study of the clinical case and oral cavity exploration

We interviewed patients' parents or guardians by a questionnaire about the history and clinical evolution, both systemic and buccal. Then, we performed an oral examination which focused on the search for the following alterations:

d) Presence of xerostomia

Initially, it was performed a clinical buccal inspection for signs of xerostomia (opaque mucosa membranes and thick saliva); it was also evaluated the mucosa-membrane hydration level as explained below:

The lower lip was turned from the inside out, the labial mucosa was carefully dried with gauze by a piece of paper over the mucosa; it was searched for saliva droplets formation by minor glands' holes.

For the quantification of the size of saliva production, we set up as parameters:

1. Low salivary production: more than four drops of saliva in sixty seconds.
2. Normal salivary production: more than four drops of saliva in sixty seconds.

For the inspection of mucosa hydration, we inspected if the tongue adheres after depression which indicates a positive sign of dehydration.

Therefore, we defined xerostomia as the existence of two positive signs found by the procedures mentioned above.

e) Oral exam of soft tissues

It was performed a detailed examination; different injuries found corresponded to the following ones:

- 1) Traumatic ulcers (14): they have a very irregular loss edge and a frequent unique random distribution.
- 2) Herpetic ulcers (14): they have a scalloped border with an erythematous area. They are usually multiple

and painful; located at the oral corners, lips, and gums.

- 3) Gingivitis (15): they are swollen and erythematous gum, sometimes painful.
- 4) Candida plaques (14): they are white cotton-like and friable regions on gums, mucosa, or tongue; they are easily removed leaving an erythematous and bleeding area.
- 5) Mucositis (16): it is an inflammation of the mucosa membranes with oral erythema, ulcers, and pain.

Gingival index (GI) (17, 18) It was based on the method described by Silness and Loe (Table 1). It is intended to record the degrees of deposit of dental-bacterial plaque

(DBP) without the need to dye it; it is calculated with the formula:

$$GI = \frac{\sum_{i=1}^n Xi}{n}$$

Where *GI* is the gingival index of each revised tooth, *n* is the number of explored surfaces, *Xi* is the presence of DBP on each studied tooth surface. We assessed DBP buildup using a dental scoop and an intraoral mirror, and we codified the findings according to Silness and Loe scale (18) (Table 1). The explored surfaces were vestibular, palatine/lingual, mesial, and distal.

Table 1: Gingival Index (GI)*

Degree	Description
0	DBP absent
1	DBP only detectable when passing the dentin spoon
2	Moderate and visible DBP
3	Abundant DBP; covers beyond the gingival third of the tooth surface

*GI: Silness and Loe gingival index for the graduation of the accumulation of dental-bacterial plaque (DBP) on the gingival surface (17, 18).

CPOD and ceod indices. They are used to show the experience of caries in a patient, whether currently or in the past; the only difference between the two is that CPOD index evaluates the permanent dentition and the ceod the deciduous dentition. In order to understand these indices, their components must be broken down: 'C' and 'c' show the decayed teeth in the permanent and deciduous dentition respectively, 'P' refers to the

permanent dentition, 'e' writes down the deciduous dentition, or the teeth lost either by caries or by extraction, 'O' denotes the clogged teeth, and 'D' means dentition. These indices are obtained from the individual sum of the values of each element (tooth): decayed, lost, and filled (CPO or ceo), which is divided by the total number of existing teeth (Table 2)(19).

Table 2: CPOD Index*

Interval	Gravity
0.0 – 1.1	Exceptionally low
1.2 – 2.6	Low
2.7 – 4.4	Moderate
4.5 – 6.5	High
>6.6	Extremely high

*CPOD: Index of decayed, lost and filled teeth(19).

f) Hemocytometry study

Consisted of a blood of carrying out the blood count. Concerning the B-cell ALL group, blood count (BC) study of each patient was conducted on those samples taken in the interval of 1 to 10 days after the first chemotherapy; BC was also checked when this treatment was not started yet. In T1DM cases, BC were taken at the time of the last medical and dental check-up; diabetes treatment had already started. BC in

healthy cases were taken during the medical or dental consultation. BC was interpreted by expert physicians based on the normal pediatric values, according to the age range established in the international parameters to Mexican patients (Appendix S2)(20).

g) Statistical analysis

We obtained simple and relative frequencies from nominal and categorical variables. Respect continuous variables, age ranges, means, and standard

deviations we used the χ^2 test for proportions to evaluate significant differences between groups, based on the SPSS-IBM 25.0 program for calculations.

III. RESULTS

This study included fifteen patients, with five children each (see methodology and Table S1).

a) Clinical Findings

Through the detailed intraoral examination, we found that 60% of both diabetic (Figure 3) and leukemic

(Figure 6) patients exhibited notorious xerostomia; this sign was negative in the healthy group (Figure 1, Table 3).

In the examination of soft tissues, we found that 80% of patients with T1DM or B-cell ALL presented some type of oral alteration; 100% of the healthy group were free of pathology (Table 4).

Table 3: Xerostomia clinical data

	Healthy	Percentage*	T1DM	Percentage	B-cell ALL	Percentage
Presence	0	0%	3	60%	3	60%
Absence	5	100%	2	40%	2	40%

*Refers to the proportion of the total number of patients in each group: healthy, T1DM (Type 1 Diabetes Mellitus) and B-cell ALL (B-cell Acute Lymphoblastic Leukemia).

Table 4: Soft tissues injuries

	Healthy	Percentage*	T1DM	Percentage	B-cell ALL	Percentage
Presence	0	0%	4	80%	4	80%
Absence	5	100%	1	20%	1	20%

*Refers to the proportion of the total number of patients in each group: healthy, T1T1DM (Type 1 Diabetes Mellitus with insulin treatment) and B-cell ALL (B-cell Acute Lymphoblastic Leukemia).

The lesions found in patients with T1DM (Figure 1) were gingivitis (40%) (Figure 2) and traumatic ulcers (40%) (Figure 3). In patients with B-cell ALL predominated: candidiasis (40%) (Figure 4), gingivitis (20%) (Figure 5), HSV-like ulcers (20%) (Figure 5), traumatic ulcers (20%) (Figure 6), mucositis (20%)

(Figure 6). Therefore, lesions in the B-cell ALL patients group were more variable than in the T1DM one; moreover, not only a greater variability but also a bigger lesions intensity were observed in the B-cell ALL group.

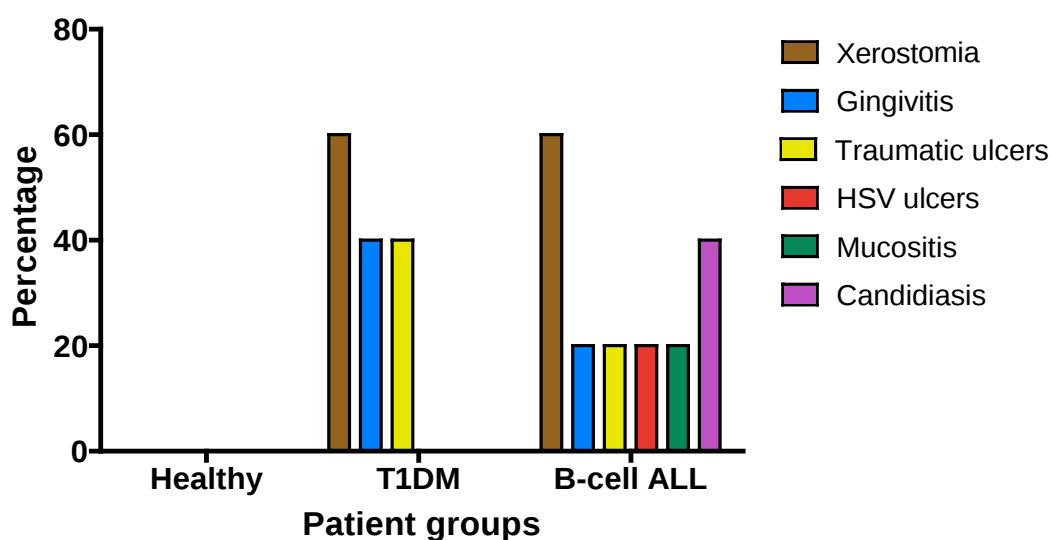


Figure 1: Frequency of oral lesions in soft tissues. T1DM (patients with Diabetes Mellitus type 1), B-cell ALL (patients with B-cell Acute Lymphoblastic Leukemia), HSV (Type 1 Herpes simplex virus).



Figure 2: Gingivitis in a patient with T1DM. The erythematous and edematous gums, especially the upper one, are clear.

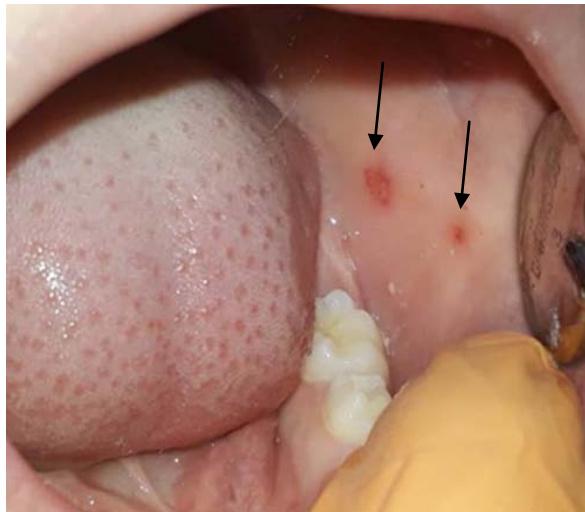


Figure 3: Oral lesions in a patient with T1DM. Xerostomia and pallor of the mucous membranes, coated tongue, flaky taste buds and the presence of 2 traumatic ulcers in the jugal mucosa are seen.



Figure 4: Candidiasis lesions in a patient with B-cell acute lymphoblastic leukemia (B-cell ALL). Pale mucous membranes are seen with the abundant presence of DBP on the tooth surfaces. Whitish lesions of fungal origin (*Candida albicans*); they are found in the gingival mucosa and the bottom of the sac of the upper arcade.

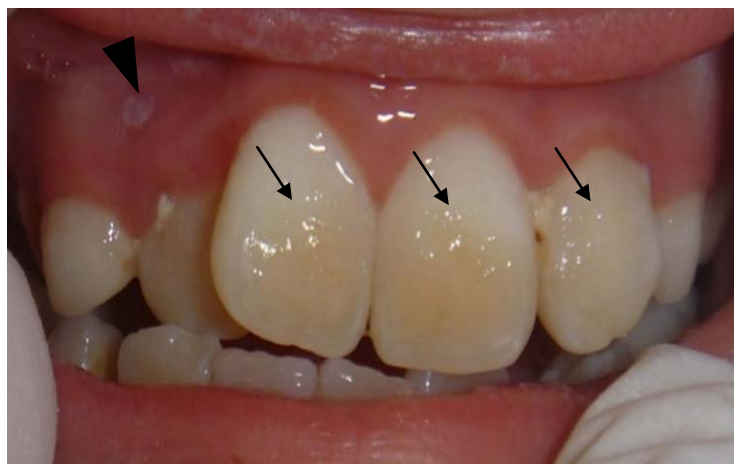


Figure 5: Soft tissue lesions in a patient with B-cell acute lymphoblastic leukemia (B-cell ALL). There is a well-delimited ulcerative HSV-like lesion of whitish coloration (arrowhead) in the swollen and erythematous gingival mucosa, and presence of dental-bacterial plaque (DBP) (arrows).

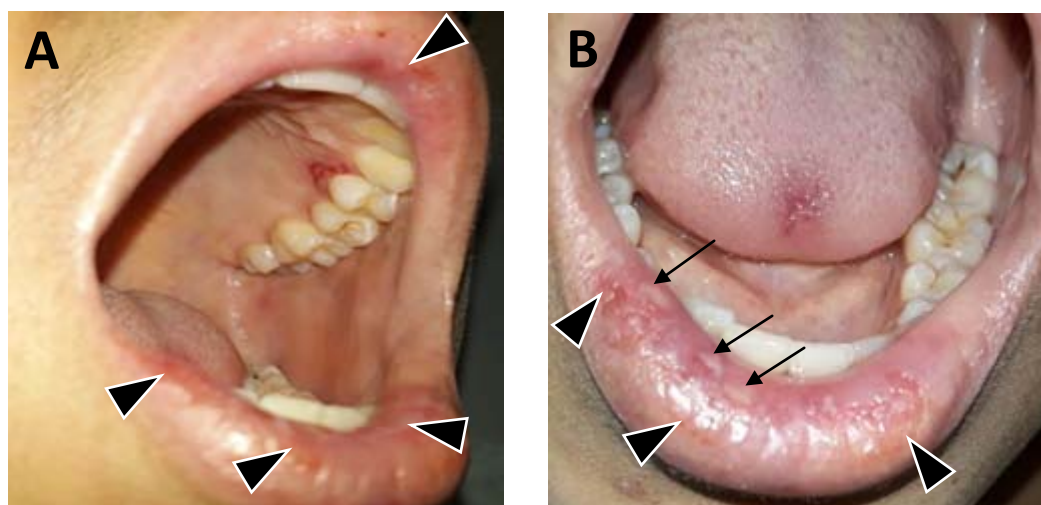


Figure 6: Oral lesions in a patient with B-cell acute lymphoblastic leukemia (B-cell ALL). In both photographs you can see different lesions: hypohydrosis and pallor of mucous membranes and multiple caries. (A) An ulcer in the palatine mucosa (arrow), secondary to mucositis; and exfoliative cheilitis (arrowheads). (B) On the back of the tongue there is an irregular ulcer with erythematous contour, secondary to mucositis; multiple HSV-like ulcers with an erythematous contour (arrows) distributed in the labial mucosa along with traumatic ulcers and exfoliative cheilitis, mainly on the external part pf the lower lip (arrowheads).

For risk of caries evaluation, we relied on the oral hygiene index standards established by Silness and Loe (50). T1DM children group presented very low values of CPOD-ceod (cariogenic risk) and GI indices (1.0 and 2.2, respectively), healthy patients group had higher risk values (3.2 and 2.7 respectively), and B-cell ALL children set had the highest ones (5.2 and 4.6 respectively) (Table 5). On the other hand, oral pH values

in B-cell ALL and healthy children groups were practically neutral (pH 7.1 and 7.0, respectively); while in the T1DM set the value was acidic (pH 6.1). Nevertheless, these values did not exceed the cariogenic threshold (pH 5.5); they were very close in the three groups. Therefore, there were no significant differences (Table S2).

Table 5: CPOD-ceod and GI indices

Groups	CPOD-ceod*	GI*	GI Interpretation
Healthy	3.2	2.7	Low
T1DM	1.0	2.2	Extremely low
B-cell ALL	5.2	4.6	High

*Mean index to evaluate decayed, missing and filled teeth (CPOD-ceod) (19) and gingival index (GI) based on Silness and Loe (18) adjusted for pediatric patients.

b) Hemocytometric Study

BC white formula showed that 100% of B-cell ALL patients presented leukopenia ($p < 0.01$) secondary to neutropenia ($p < 0.01$) and lymphopenia ($p < 0.01$);

there were not anomalous counts in other morphologically normal leukocytelines. There were no leukocyte alterations in healthy and diabetic groups either (Tables 6 and 7).

Table 6: Findings in the white formula of the distinct groups of patients*

Alteration	Healthy	Percentage	T1DM	Percentage	B-cell ALL	Percentage
Leukopenia	0	0%	0	0%	5	100%
Neutropenia	0	0%	0	0%	5	100%
Lymphopenia	0	0%	0	0%	5	100%
Eosinophilia	0	0%	0	0%	0	0%
Monocytosis	0	0%	0	0%	0	0%

*The percentage refers to the proportion of the total number of patients in each group with some alteration. Groups: Healthy (healthy children), T1DM (Type 1 Diabetes Mellitus), B-cell ALL (B-cell Acute Lymphoblastic Leukemia).

Table 7: Stratified of the hematic characteristics by nosological entity in children and adolescents with oral lesions

	Healthy n (%)	T1DM n (%)	B-cell ALL n (%)	p^*
Leukopenia				
Present	0 (0.0)	1 (20.0) 4 (80.0)	5 (100.0)	0.003
Absence	5 (100.0)	0 (12.5) 5 (100.0)	0 (0.0)	
Neutropenia				
Present	0 (0.0)	0 (12.5) 5 (100.0)	5 (100.0)	0.001
Absence	5 (100.0)	0 (0.0) 5 (100.0)	0 (0.0)	
Lymphopenia				
Present	0 (0.0)	0 (0.0) 5 (100.0)	5 (100.0)	0.001
Absence	5 (100.0)	0 (0.0) 5 (100.0)	0 (0.0)	
Eosinophilia				
Present	0 (0.0)		0 (0.0)	1.0
Absence	5 (100.0)		5 (100.0)	
Monocytosis				
Present	0 (0.0)		0 (0.0)	1.0
Absence	5 (100.0)		5 (100.0)	
Anemia				
Present	0 (0.0)		3 (60.0)	0.02
Absence	5 (100.0)		2 (40.0)	

*p-value confirmed by Pearson's χ^2 method for proportions; a p-value less than 0.01 is considered significant. Study groups: healthy (healthy) children, children with Type 1 Diabetes Mellitus (T1DM) or B-cell Acute Lymphoblastic Leukemia (B-cell ALL).

BC red formula showed that all B-cell ALL children presented anemia; four patients had macrocytic hyperchromic anemia (80%) consistent with megaloblastic anemia; anisocytosis was reported in 1 case (Table 8).

*Table 8: Presence of anemia in distinct groups of patients**

Type of Anemia	Healthy	T1DM	B-cell ALL	Diagnosis
Hyperchromic Macrocytic	0	0	4 (80%)	Megaloblastic anemia
Hyperchromic Normocytic	0	0	1 (20%)	Anisocytosis
Hypochromic Microcytic	0	0	0	Iron Deficiency Anemia

*T1DM (Type 1 Diabetes Mellitus), B-cell ALL (B-cell Acute Lymphoblastic Leukemia).

IV. DISCUSSION

In this study, we performed a global clinical analysis of the oral cavity with the end to identify diverse types of lesions as well as oral cavity hygiene, caries, and tooth losses. We also evaluated the blood tissue state basing us on BC studies. All these parameters were carried out in three groups of pediatric patients: healthy, T1DM, and B-cell ALL (Table S1).

Regarding the clinical analysis, lesions were found in T1DM and B-cell ALL groups; except for poor oral hygiene, the healthy group did not present pathological alterations were found. Respect oral hygiene, T1DM patients had the best CPOD-ceod and GI indices (Table 5) whereas B-cell ALL children revealed the worst ones. These findings can be explained by the fact that diabetic patients eat less sugary foods, and generally receive more oral care than most patients; obviously, the more oral hygiene the fewer complications (21). The most precarious oral hygiene in the B-cell ALL group can be understood as consequence of an important pain presence due to epithelial fragility occasioned by both mucositis -caused by chemotherapy (22)- and leukemia per se. The pain also causes a less teeth brushing frequency, leading to a higher GI (measure of DBP formation) and CPOD-ceod (measure caries and teeth losing) indices (Table 5).

Xerostomia, in general, is more pronounced in Diabetes Mellitus which it was also observed in our T1DM group; it is consequence of the chronic hypohydration state specially seen in poorly controlled patients (23). This, in the long run, will reduce non-immunological defense barriers such as:

1. Physical barriers: saliva will turn more viscous which will decrease an efficient oral mechanical washing (24).
2. Chemical barriers: salivary hyperviscosity is consequence of the high glucose and electrolyte (calcium and phosphorus) concentrations which occasions a pH decrease and it also affects the enzymatic functions (amylase an alkaline phosphatase) (25).

3. Biological barriers: physicochemical alterations of microenvironment alter the oral microbiota composition and, therefore, favor growth of pathogenic and opportunistic microorganisms (24).
4. Immune barriers: the increased oral viscosity and abnormal pH will occasion immune dysfunctions, specifically in the antibodies (26, 27). Diabetic microangiopathy significantly affects the immune function; however, it is not a factor to take into account in our group since this is a long-term complication.

However, there were a lower CPOD-ceod index (lesser caries) in T1DM group than in the healthy set despite of the first one had oral lesions. This can be explained because of the higher tooth washing frequency and lower carbohydrates intake (candies and chocolates especially) by T1DM children.

B-cell ALL group also presented a greater quantity and variety of lesions which were more severe. Like in T1DM, it was detected gingivitis and traumatic ulcers along with exfoliative cheilitis (Figures 5 and 6) and other lacerations: oral candidiasis (Figure 4), herpetic ulcers (Figure 6), and mucositis (Figure 6). Basing us on the underlying disease's natural history, treatment, and BC results, we suggest that the most relevant lesion-generating factor was the immunosuppression state in this group. So, oral alterations secondary to B-cell ALL pathophysiology can be explained as follows:

The underlying nosological entity itself. The lymphoblastic neoplasm grows in the red bone marrow, so it displaces healthy tissue which is occupied by are non-functional blast cells both in the bone marrow and peripheral blood. Paradoxically, the hemocytometry values of the white formula will be extremely high; however, normal leukocyte counts will be low.

Chemotherapy. Sant Jude 16 protocol (12, 13) (see methodology and Appendix S3), not only kills neoplastic cells but also functional ones which aggravates the state of immunosuppression. In addition treatment is also involved not only in the treatment but also triggering mucositis which turns the mucosa pretty fragile (22). On the other hand, bone marrow damage caused by both leukemia and

chemotherapy affect platelet and erythrocyte production causing thrombocytopenia and anemia (megaloblastic anemia) which was proved in the BC (Table 8). This last finding is mainly triggered by methotrexate administration -part of the Saint Jude 16 therapeutic protocol- which is a folic acid antagonist (28).

Oral pH revealed a neutral value in B-cell ALL and healthy patient groups (pH 7.1 and 7.0 respectively); pH in T1DMset was acidic (pH 6.1) (Table S2). However, this record did not reach a critical value (pH ≤ 5.5) to be considered as a cariogenic factor (29). Therefore, CPOD-ceod and Glindices suggest the cariogenic risk is related to other factors such as poor oral hygiene; especially in B-cell ALL children, probably related to the frequent oral pain.

It is also pertinent to clarify that, at the moment, our sample size is small, so we will continue increasing the number of samples of each group to increase the statistical power.

V. CONCLUSIONS

Both B-cell ALL and T1DM are one of the more important systemic diseases in pediatric age which also have a significant impact on the oral cavity. Prominently, the key factor related to B-cell ALL is immuno-compromise, provoked by both the neoplastic disease and chemotherapy, whereas in T1DM the main disbalance is ametabolic dehydration and hyperglycemic state. The lowest presence of caries (lower CPOD-ceod index) in the T1DM group is linked to the better oral hygiene associated in the treatment. Finally, our results suggest that systemic diseases alter the buccal cavity homeostatic state, affecting the normal-microbiota development, favoring pathogenic or opportunistic microorganisms' grow and attack(30) and an increase of systemic-infections risk and septicemia (31); so, we suggest that underlying diseases like B-cell ALL and T1DM, and their treatments effects, have a relevant impact in the oral cavity homeostasis as well as over microbiota composition; all this together leads to the formation of oral lesions. Therefore, we propose that it is especially important to carry out metagenomic studies (gene-taxonomy with last generation sequencing) of the oral microbiota to identify specific changes that could specifically identify those pathogenic species that cause oral lesions formation.

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SUPPLEMENTARY TABLES

Table S1: Study groups analyzed for oral lesions

Group	Clinical diagnosis	Number of patients	Men	Women	Interval (years)
1	T1DM	5	2	3	5-15
2	B-cell ALL	5	2	3	5-15
3	Healthy	5	2	3	5-15
Total		15	6	9	

Abbreviations: T1DM (Diabetes Mellitus type 1 with insulin treatment), B-cell ALL (B-cell Acute Lymphoblastic Leukemia with chemotherapy in the induction to remission phase).

Table S2: Oral pH values

Groups	pH	Interpretation*
T1DM	1.0	Not cariogenic
B-cell ALL	5.2	Not cariogenic
Healthy	3.2	Not cariogenic

*The cariogenic risk was considered when pH<5.5.

SUPPLEMENTARY APPENDICES

Supplementary Appendix S1

A) Inclusion criteria

Group of patients with T1DM: confirmed diagnostic of DM1, insulin treatment already set up. Recent complete blood count (BH) (less than 2 weeks). Age range: 5 to 15 years.

Group of patients with B-cell ALL: Confirmed diagnosis of B-cell or pre B-cell, which will be described together as B-cell ALL. Patients in the induction to remission phase of chemotherapy. Recent full BH (less than 2 weeks). Age range: 5 to 15 years.

Control group of healthy children: Age and gender comparable with the groups of B-cell ALL and T1DM. Recent full BH (less than 2 weeks). Hospitalized for trauma-related treatments (fractures, dislocations). Age range: 5 to 15 years.

B) Exclusion criteria

Group of patients with T1DM: Patients outside the age range. Not having written informed consent. Patients with oral appliances. Infectious diseases in the last 4 weeks. Antibiotic therapy 2 weeks prior to sampling.

Group of patients with B-cell ALL: Patients outside the age range. Patients in the consolidation or maintenance phase in their chemotherapy treatment. Not having written informed consent. Patients with oral appliances. Patients with Burkitt lymphoma. Infectious diseases in the last 4 weeks. Antibiotic therapy 2 weeks prior to sampling.

Control group of healthy children: Presence of systemic diseases. Presence of some concomitant syndromes. Not having written informed consent. Patients with oral appliances. Infectious diseases in the last 4 weeks. Antibiotic therapy 2 weeks prior to sampling.

Supplementary Appendix S2

Blood Count Normal pediatric values. According to the patients' age, and established in the international weighting tables adapted to Mexican patients (20).

Table S3: Red blood cells

Age	1-13 d	14-60 d	3 m-10 y	11-15y	Adults
Erythrocytes* (millions/mm ³)	5.1±1.0	4.7 ± 0.9	4.5± 0.7	4.8	5.4 ± 0.9 M 4.8 ± 0.6 W
Hemoglobin* (g/dL)	19.5 ± 5.0	14.0 ± 3.3	12.2 ± 2.3	13.4	16.0 ± 2.0 M 14.0 ± 2.0 W
Hematocrit* (percentage)	54.0 ± 10.0	42.0 ± 7.0	36.0 ± 5.0	39.0	47.0 ± 5.0 M 42.0 ± 5.0 W
MCV (fL)	98-106	90	80	82	90 ± 7 M 90 ± 7 W
MCH (pg)	33-38	30	27	28	29 ± 2 M 29 ± 2 W
CHMC (g/dL)	34-36	33	34	34	34 ± 2 M 34 ± 2 W
MCD (µm)	8.6	8.1	7.7		7.5 ± 0.3 M 7.5 ± 0.3 W

*The values range represents variation extremes (93%) at sea level.

Abbreviations: MCV (mean corpuscular volume), MCH (medium corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), MCD (mean corpuscular diameter); d (days), m (months), y (years), M (men), W (women).

Table S4: White blood cells

Age	1 y	4 y	6 y	10 y	Adult (>21 y)
Total* Leucocytes	11,400 (6.0-17.5 K) 100%	9,100 (5.5-15.5 K) 100%	8,500 (5.0-14.5 K) 100%	8,100 (4.5-13.5 K) 100%	7,400 (4.5-11.5 K) 100%
Neutrophils Total*	3,500 (1.5-8.5 K) 31%	3,800 (1.5-8.5 K) 42%	4,300 (1.5-8.0 K) 51%	4,400 (1.8-8.0 K) 54%	4,400 (1.8-7.7 K) 59%
Bands*	350 3.1%	270 3.0%	250 3.0%	240 3.0%	220 3.0%
Segmented*	3,200 28%	3,500 39%	4,000 48%	4,200 51%	4,200 56%
Lymphocytes*	7,000 (4.0-10.5 K) 61%	4,500 (2.0-8.0 K) 50%	3,500 (1.5-7.0 K) 42%	3,100 (1.5-6.5 K) 38%	2,500 (1.0-4.8 K) 34%
Monocytes*	550 (0.05-1.1 K) 4.8%	450 (0-0.8 K) 5.0%	400 (0-0.8) 4.7%	350 (0-0.8 K) 4.3%	300 (0-0.8) 4.0%
Eosinophiles*	300 (0.5-0.7 K) 2.6%	250 (0.02-0.65 K) 2.8%	230 (0-0.65 K) 2.7%	200 (0-0.6 K) 2.4%	200 (0-0.45 K) 2.7%
Basophiles*	50 (0-0.2 K) 0.4%	50 (0-.2 K) 0.6%	50 (0-.2 K) 0.6%	40 (0-.2 K) 0.5%	40 (0-0.2 K) 0.5%

Values in the first line of each row are expressed as 10^3 cells/ μ L. Abbreviations: y (years), K (10^3).