Original Article

Oral health of pediatric liver transplant recipients

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Abstract
To evaluate oral health conditions in pediatric liver transplant recipients, with special focus on caries, green staining of the teeth, gingival bleeding, and gingival overgrowth. 40 patients (mean age 11.6 years) were examined at a routine follow-up visit, 6 months to 16 years after liver transplantation at the Swiss Center for Liver Disease in Children. After the medical examination, participants were further examined for the presence of dental caries, periodontal disease, GE, and GTC. The mean decay, missing, and filled teeth (dmft/DMFT) score was 3.8. 45% of the participants presented at least one carious lesion. Two-third of the participants had more than 20% of sites with the presence of plaque and gingival inflammation. Signs of GE were found in 18% and GTC in 30% of the participants. A positive correlation was identified between GTC and peak serum bilirubin (P<.001) and primary diagnosis of cholestatic disease (P=.04). Gingival inflammation was associated with plaque (P<.001), use of immunosuppressive medication (P=.04), and was more pronounced in children with cholestatic disease (P=.007). Children and young adults with liver transplants presented a rather poor oral health status. Liver transplant physicians should counsel patients for regular dental follow-up in order to avoid serious dental infections.

Keywords
caries, dental care, gingival enlargement, gingivitis, greenish tooth coloration, liver transplantation

1 | Introduction

Dental caries and periodontal diseases are among the most common chronic diseases of mankind. They have a negative impact on quality of life and are the principle reasons for losing teeth. In caries, the teeth are damaged by bacteria fermenting dietary sugars to organic acids. In periodontal diseases, specialized members of the oral microbiota dysregulate the host immune response, which results in destruction of the tissues anchoring the teeth in the bone, that is, the periodontium. Lifestyle behaviors such as poor oral hygiene, a diet rich in carbohydrates, and smoking are risk factors for these diseases. There is an association between several systemic conditions, notably diabetes, coronary heart disease, and adverse pregnancy outcomes, and the diseases of the periodontium. The release of oral bacterial metabolites into the bloodstream and the activation of the host inflammatory and immune response are thought to be the main mechanism responsible for this association. Thus, infected teeth may add to the overall systemic inflammatory burden in the body. This effect is further enhanced in patients under immunosuppressive regimen used for the management of a wide variety of medical conditions, including after LT. With this in mind, it is important to highlight that there is not only a risk of transient bacteremia but also of septicemia. Infections are a major concern after LT. Although the long-term survival of pediatric LT recipients is no longer questioned, infections are still a frequent cause of morbidity. Both children and adults following LT have been reported to have poor oral health. Common findings in

Abbreviations: CsA, cyclosporine; DMFT, decay, missing, and filled teeth; GE, gingival enlargement; GI, gingival index; GTC, greenish tooth coloration; HyB, hyperbilirubinemia; LT, liver transplantation; PD, probing depth; PI, plaque index; TAC, tacrolimus.
children after LT include a high prevalence of caries, green staining of the teeth, gingival bleeding, gingival overgrowth, and enamel hypoplasia.\textsuperscript{7-10} In adults, edentulism, periodontitis, periapical lesions, abscesses, xerostomia, oral candidiasis, and high prevalence of caries have been reported following LT.\textsuperscript{11-13} These studies suggest that preventive dental care and control of oral disease should be a high priority in LT patients.

However, in order to offer the most efficient preventive care, it is necessary to have a better understanding of the relative contribution of various factors. With regard to gingival inflammation, it is known that the accumulation of bacterial deposits on teeth causes gingivitis, but other aspects also play a role, as witnessed, for example, by an increased tendency for gingival inflammation during pregnancy\textsuperscript{14} and with the association between salivary estrogen levels and extent of inflammation.\textsuperscript{15}

In the context of the present study, oral health conditions in LT patients may depend on the quality of oral hygiene as well as on various elements of the medical history and past or current medications.

The aim of this cross-sectional study was to evaluate oral health conditions in children living in Switzerland with liver transplants, with a special focus on caries, green staining of the teeth, gingival bleeding, gingival overgrowth, and to assess the relative contribution of oral health behaviors and factors related to liver disease and therapy.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a single-center, cross-sectional cohort study. The Ethical Committee of the University Hospitals of Geneva, Geneva, Switzerland, approved the study. Informed consent was obtained from the patients, parents, or guardians of the participants of the study.

Between June 2013 and February 2014, we examined 40 children and young adults (17 males, 23 females) aged 4-22 years (mean age: 11.6 years) 6 months to 16 years after LT at the University Children's Hospital of Geneva. The participants were examined according to standards of care at a scheduled follow-up visit during which routine follow-up laboratory tests of liver function and immunosuppression were carried out. All patients with more than 1 year post-LT and older than 4 years of age were offered a dental examination as part of their routine, annual follow-up visit. Patients requiring treatment for rejection at the time of the study or patients with leukopenia (<4 G/L) were excluded. The medical and dental histories were assessed using structured questionnaires. A physical examination was also carried out. Clinical and radiographical dental examinations were performed to assess for the presence of dental caries, periodontal diseases, GE, and GTC.

2.2 | Medical visit

Data concerning the indication for LT, the date of transplantation, the immunosuppressive regimen (CsA, TAC with trough levels), and markers of hepatic function were obtained retrospectively by chart review from previous routine follow-up visits or hospital stays. The use of other medications, especially steroids, mycophenolate mofetil, calcium channel blockers, and antihypertensive agents, such as nifedipine, was recorded.

2.3 | Oral examination

Two trained and calibrated dental practitioners (MJ.S and A.Z) performed the oral examinations on the same day as the medical and laboratory examinations. Information was obtained by questionnaire regarding the oral health history, the utilization of dental care services, and oral hygiene habits. Dental caries was assessed using the DMFT index (dmft for the primary dentition, DMFT for permanent teeth), a well-established tool for assessing dental treatment needs. This index simply counts the number of decayed, missing due to caries, and restored teeth in a dentition.\textsuperscript{16} The presence of plaque and gingival inflammation were assessed using the PI, and GI, respectively. PI score and GI score between 0 and 3 were given for the distal, buccal, mesial, and lingual/palatal surfaces of each erupted primary and permanent tooth as follows: PI score 0: no plaque; 1: plaque only visible on probing; 2: moderate soft deposits visible by naked eye; 3: abundant soft matter.\textsuperscript{17} GI score 0: absence of inflammation; 1: mild inflammation, slight redness, slight edema, and no bleeding on probing; 2: moderate inflammation, redness, edema, and bleeding on probing; 3: severe inflammation, marked redness, edema, and tendency to spontaneous bleeding.\textsuperscript{18}

Periodontal PD was assessed in millimeters (mm) by inserting a graded periodontal probe (HuFriedy, PCP12, Frankfurt am Main, Germany) with light pressure into the gingival crevice at four sites around eight permanent teeth, that is, the four central incisors (tooth numbers 11, 21, 31, and 41) and the four-first molars (tooth numbers 16, 26, 36, and 46).

To assess the presence of GTC, we created an index ranging from 0 to 2. The following scores were given to each tooth according to consensus reached by the two clinical examiners: score 0: no coloration; 1: mild greenish coloration; 2: severe greenish coloration (Figure 1). To assess GE, the interdental papilla and gingival margins of the primary and permanent teeth were examined on the distal, buccal, mesial, and lingual/palatal surfaces for absence or presence of gingival enlargement. Teeth were evaluated according to the following criteria: score

![No coloration (0)](image1)
![Mild tooth coloration (1)](image2)
![Severe tooth coloration (2)](image3)

**FIGURE 1** Greenish tooth coloration evaluated by two calibrated examiners.
No coloration (0) Mild tooth coloration (1) Severe tooth coloration (2)
0: no enlargement; 1: slight or moderate enlargement (≤2 mm); 2: severe enlargement (>2 mm).

Intraoral photographs and radiographs (bitewings and/or panoramic radiographs according to the patient’s age) were taken to evaluate the presence of interproximal carious lesions.

2.4 | Statistical analysis

The data were analyzed descriptively. We used percentages, means, and standard deviations for the clinical characteristics. The association between medical disease characteristics, such as bilirubin peak (mcmol/L), age of bilirubin peak and medication (CsA, TAC, and nifedipine), and the clinical characteristics, such as GTC, DMFT, GE, PI, and GI scores, was analyzed using Spearman’s correlations. The same data were further analyzed in a subgroup of patients with cholestatic disease diagnosis. To determine whether medical disease characteristics have a direct impact on clinical characteristics, we used multivariable regression analyses to predict clinical characteristics, adjusting for time since LT, PI, immunosuppressive regimen, and peak bilirubin. All analyses were performed using R v3.3.2 (R Foundation, Vienna, Austria), and P values <.05 were accepted for statistical significance.

3 | RESULTS

The demographic and medical characteristics as well as the transplant-related history of the participants are shown in Table 1. The sample had a male/female ratio of 1/1.3, 50% were over the age of 12 years, and 70% were of European origin. The primary diagnosis for LT was mainly biliary atresia (57.5%), followed by other causes of cholestasis (22.5%). The majority of children (90%) underwent LT for more than 2 years before dental examination. Twenty-four children (60%) had experienced acute graft rejections requiring steroid therapy; 19 of them had experienced one and five had experienced multiple episodes.

The oral health behavior and the clinical characteristics of the patients are shown in Table 2. Twenty-two children (55%) had seen a dentist in the past 6 months, and two children (5%) reported to have never seen a dentist. The frequency of tooth brushing varied between once a day (32.5%), twice daily (40.0%), and >2 times daily (27.5%).

| Table 1 | Characteristics of 40 pediatric liver recipients. Data are numbers of participants (percent) |
|---------|-------------------------------------------------------------------------------------------|
| Gender  | Females 23 (57.5)                                                                         |
| Age (y) | < 6 6 (15.0)                                                                          |
|         | 6-12 14 (35.0)                                                                         |
|         | >12 20 (50.0)                                                                          |
| Ethnicity | European 28 (70.0)                                                                       |
|         | African 4 (10.0)                                                                         |
|         | Asian 1 (2.5)                                                                           |
|         | American 1 (2.5)                                                                        |
|         | Mixed 6 (15.0)                                                                          |
| Primary diagnosis for liver transplantation | Biliary atresia 23 (57.5) |
|         | Other cholestasis 9 (22.5)                                                              |
|         | Tumors 3 (7.5)                                                                          |
|         | Metabolic liver disease 3 (7.5)                                                          |
|         | Acute liver failure 2 (5.0)                                                              |
| Time since liver transplantation (years) | ≤ 2 4 (10.0)                                                                          |
|         | > 2 36 (90.0)                                                                          |
| History of acute rejection | Yes 24 (60.0)                                                                          |
| Episodes of acute rejection (n=24) | 1 x 19 (79.2)                                                                           |
|         | 2 x 2 (8.3)                                                                            |
|         | 3 x 3 (12.5)                                                                            |

| Table 2 | Oral health behavior and clinical characteristics. Data are numbers of participants (percent) |
|---------|-------------------------------------------------------------------------------------------|
| Time since last dental visit | <6 mo 22 (55.0) |
|         | 6-12 mo 10 (25.0)                                                                        |
|         | >1 y; <2 y 2 (5.0)                                                                       |
|         | ≥2 y 4 (10.0)                                                                           |
| Never visited a dentist | 2 (5.0) |
| Tooth brushing frequency | Once a day 13 (32.5) |
|         | Twice daily 16 (40.0)                                                                    |
|         | >2 times daily 11 (27.5)                                                                 |
| Untreated caries | 1-4 13 (32.5) |
|         | 5-8 3 (7.5)                                                                             |
|         | ≥9 2 (5.0)                                                                              |
| Treated caries | 1-4 15 (37.5) |
|         | ≥5 9 (22.5)                                                                             |
| DMFT/dmft | 0 7 (17.5) |
|         | 1-4 19 (47.5)                                                                           |
|         | 5-8 11 (27.5)                                                                           |
|         | ≥9 3 (7.5)                                                                              |
| PI | mean PI ≥1 27 (67.5) |
|         | >20% sites with PI >1 23 (57.5)                                                          |
| GI | mean GI ≥1 32 (80.0)                                                                    |
|         | >20% sites with GI >1 24 (60.0)                                                          |
| GE | GE >0 7 (18.0)                                                                          |
| Tooth coloration | GTC >0 12 (30.0) |

DMFT, decayed, missing, and filled teeth; PI, plaque index; GI, gingival index; GE, gingival enlargement; GTC, greening tooth coloration.
GE were under TAC exclusively, three others used a double immunosuppressive regimen combining TAC and mycophenolate mofetil, and the last one had recently switched his immunosuppressive medication from CsA to TAC. No patient using nifedipine as antihypertensive medication presented GE.

A greenish coloration of teeth was observed in 12 participants. In five of them, all teeth were affected, and in the other seven, the coloration concerned 4-89% of the teeth. According to the GTC index, severe coloration (score 2) was observed in 52% of the affected teeth, while the others (48%) presenting mild coloration (score 1). Both primary and permanent dentitions were affected (Figures 3-4). No child presented clinical signs of candidiasis.

Table 3 shows the associations between medical disease characteristics (overall and among cholestatic subjects) and the clinical oral parameters. Positive correlations were observed between GTC and peak serum bilirubin pre- LT, initial cholestatic diagnosis, and GI. Among the cholestatic subjects, GTC was positively correlated with peak of bilirubin and age of peak bilirubin. GE was correlated with the age of peak bilirubin, and GI >1 was correlated with the diagnosis of cholestatic disease, the type of the immunosuppressive regimen (CsA or TAC), the TAC trough levels, and the PI. Results remained relatively similar in the adjusted analyses (adjusted for PI, immunosuppressive treatment, and time since LT), with peak bilirubin still highly predictive of GTC ($P < .001$). The associations between peak bilirubin and either GE or GI >1 were still nonsignificant after adjustment. In these models, the PI was significant predictor of GI >1 ($P < .001$) and GE ($P = .02$), and the type of medication was significant predictor of GI >1 ($P = .02$).

**FIGURE 2** Correlation between percentage of sites with GI >1 and PI >1

**FIGURE 3** Female patient, age of 5 years, with greenish tooth coloration in primary dentition. Peak of bilirubin and liver transplantation occurred at the age of 10 months

**FIGURE 4** Male patient, age of 10 years, with greenish tooth coloration in permanent dentition. Peak of bilirubin and liver transplantation occurred at 3.5 years of age. Note resin veneers on superior incisors placed for esthetic reasons

4 | DISCUSSION

It is commonly accepted that adult patients with liver disease undergoing liver transplant benefit from oral health assessment and management both pre- and post-transplant. Less is known in children, although two recent studies comparing the oral health status in children with LT to a group of healthy individuals of similar age demonstrated a high prevalence of oral health issues. In the first study, conducted in Italy,8 all dental and periodontal parameters, including caries prevalence, dental enamel defects, mean dmft value (2.26 vs 0.69), plaque, calculus, and bleeding on probing, were significantly higher in the LT group as compared to a healthy control group. In the second study, carried out in Israel,19 lower mean dmft/DMFT and higher mean GI and calculus scores were reported in the LT compared to the control group. However, mean DMFT was low in both groups (0.122 vs 0.246).

In the present study, almost all individuals with LT examined showed signs of gingival inflammation that were associated with macroscopically visible deposits of bacteria, that is, dental plaque, and half of them presented at least one carious lesion. GE and GTC were found in 18% and 30% of the participants, respectively.

Specifically, mean dmft/DMFT in the present study was 3.80. In another Swiss study, the DMFT in the permanent dentition of healthy participants aged between 8 and 14 years ranged from 0.21 to 1.52.20 However, children who had immigrated to the country at an age >5 years were excluded from that analysis. A recent study on Swiss and non-Swiss children in the French speaking part of Switzerland reported a worrying 24.8% prevalence rate for early childhood caries, with high rates especially among children with a low socioeconomic background.21 In our cohort, two children of African origin had 11 and 12 carious lesions, respectively. The former presented 39% teeth with
The influence of plaque on the induction of gingival enlargement by these drugs has not been fully elucidated. However, it seems that the severity of the lesion is affected by the oral hygiene and the presence of plaque. More recently, gingival overgrowth has been assessed in transplant children under either CsA or TAC. GE was present in 35% of the children under CsA, but in none under TAC. A cross-sectional study investigated the effects of CsA given in conjunction with a low dose of steroids on the gingival status of pediatric patients following liver transplantation. Dental findings were compared to those from a healthy control group matched for age and sex. Although all clinical parameters were significantly higher in the liver transplant children, as compared to the healthy group, the authors reported no significant correlation between CsA serum levels and any of the dental parameters measured. In our sample, 36 from the 40 patients were using TAC as immunosuppressive medication and only four patients were under CsA. From the seven patients with GE, three were under TAC exclusively, three others used a double immunosuppressive regimen with the association of TAC and mycophenolate mofetil, and the last one had recently switched his immunosuppressive medication from CsA to TAC. Thus, for the first time, TAC regimen was associated with GE. No patient using nifedipine as antihypertensive medication presented GE.

Concerning GTC, we found that greenish coloration was present in 30% of the children and affected both primary and permanent dentition. Interestingly, five of 12 children had all their teeth stained, and more than half of them presented severe GTC. We also found a positive correlation between the GTC and the peak of bilirubin and cholestatic diagnosis. Furthermore, peak bilirubin was found to be highly predictive of GTC (P < .001) in the adjusted analyses (adjusted for PI, immunosuppressive treatment, and time since LT). The initial diagnosis for LT was mainly biliary atresia and Alagille syndrome. This is in accordance with previous studies showing that 50% of the children with HyB and biliary atresia exhibit a marked greenish coloration. In fact, biliary atresia and hemolytic disease have been reported as the main causes of the HyB-related discoloration.

### TABLE 3

Association of disease characteristics with GTC, GE, GI >1, and PI >1 using Spearman’s correlations

|                         | GTC       | GE        | GI >1      | PI >1      |
|-------------------------|-----------|-----------|------------|------------|
|                         | cor   P   | cor   P   | cor   P   | cor   P   |
| Overall                 |         |           |            |            |
| Peak bilirubin          | .63 .001 | -.13 .44  | -.29 .07  | -.33 .04  |
| Age peak bilirubin      | .28 .09  | .46 .003  | .14 .39   | .19 .25   |
| Cholestatic disease     | .32 .04  | -.14 .39  | -.42 .007 | -.29 .07  |
| CsA vs. TAC treatment   | .21 .19  | -.10 .55  | -.33 .04  | -.04 .82  |
| Tacrolimus trough levels| .21 .23  | -.14 .40  | -.42 .01  | -.08 .63  |
| Nifedipine              | .19 .23  | -.13 .42  | -.06 .72  | -.01 .96  |
| PI >1                   | -.14 .40 | .13 .43   | .70 <.001 |           |
| GI >1                   | -.38 .02 | .10 .56   |           | .68 <.001 |
| Among cholestatic       |         |           |            |            |
| Peak bilirubin          | .63 .001 | -.00 .98  | -.08 .67  | -.24 .18  |
| Age peak bilirubin      | .53 .002 | .47 .008  | -.10 .59  | .01 .94   |

Values in boldface: significant correlations (P < .05).

GTC, greenish tooth coloration; GE, gingival enlargement; GI, gingival index; PI, plaque index.
of the teeth (58.1% and 30.2% of the children, respectively).31 In a similar study to ours, Lin et al.7 (2003) reported a high prevalence of caries (61.8%) and high prevalence of green staining of the teeth (61.3%) in young children with biliary atresia. Serum bilirubin levels were significantly higher in the green-stained group than in the non-stained group. Given that serum conjugated bilirubin levels are commonly accepted to be the hallmark of liver disease severity, this finding suggests a correlation between the severity of disease and degree of tooth staining. Clinical and experimental studies have identified serum bilirubin deposits in hard and soft tissues of the body. Soft tissue turnover leads to the elimination of these deposits following remission of the metabolic defect. This is not the case for hard dental tissues where bilirubin is trapped permanently due to the loss of the metabolic activity after their maturation.30,32

In conclusion, the results of this study add to the body of literature supporting the observation that there is a high prevalence of carious lesions, plaque, and gingival inflammation in post-LT pediatric recipients. Transplant children should be monitored closely with respect to dental care during both the pretransplantation and post-transplantation period in order to avoid serious dental infections. Furthermore, the side effects of chronic liver disease on dentition may be irreversible and be aggravated by the chronic drug treatment. Thus, specific recommendations should be given to pediatric and/or general dentists of how to manage this medically compromised population. LT physicians should counsel patients for regular dental follow-up.

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AUTHORS’ CONTRIBUTIONS
Maria José Sandoval made substantial contribution to acquisition, analysis, and interpretation of the data; critically revised the manuscript; and approved the final version. Alkisti Zekeridou made substantial contribution to acquisition, analysis, and interpretation of the data; critically revised the manuscript; and approved the final version. Vasiliki Spyropoulou made substantial contribution to acquisition of the data, critically revised the manuscript, and approved the final version. Delphine Courvoisier made substantial contribution to data analysis, critically revised the manuscript, and approved the final version. Andrea Mombelli made substantial contribution to study design, analysis, and interpretation of the data; drafting the manuscript; and approved the final version. Catherine Giannopoulos made substantial contribution to study design, analysis, and interpretation of the data; drafting the manuscript; and approved the final version.

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