Oral Health-Related Quality of Life After Allogeneic Bone Marrow Transplantation—A Clinical Study

Nina Vovk , Manca Urek , Ksenija Cankar , Lidija Nemeth *

Posted Date: 9 January 2025

doi: 10.20944/preprints202501.0698.v1

Keywords: dental caries; oral health related quality of life; xerostomia; bone marrow transplantation; saliva; graft-versus-host disease; haematology; clinical study

Article

Oral Health-Related Quality of Life After Allogeneic Bone Marrow Transplantation—A Clinical Study

Nina Vovk [1], Manca Urek [2], Ksenija Cankar [3] and Lidija Nemeth [1,4,*]

[1] Department of Dental Diseases and Normal Dental Morphology, Faculty of Medicine, University of Ljubljana, 1000 Ljubljana, Slovenia 1; nina.vovk@mf.uni-lj.si

[2] Dental Center Osovnikar, 4220 Škofja Loka, Slovenia 2; manca.urek@gmail.com

[3] Institute of Physiology, Faculty of Medicine, University of Ljubljana, 1000 Ljubljana, Slovenia; ksenija.cankar@mf.uni-lj.si

[4] Division of Stomatology, University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia

* Correspondence: lidija.nemeth@mf.uni-lj.si; Tel.: +386-1-522-4255

Abstract: Background/Objectives: The aim of the study was to assess oral health-related quality of life in patients with chronic graft-versus-host disease after allogeneic haematopoietic bone marrow transplantation. **Methods**: A clinical examination was carried out on 23 patients, aged 42.28 ± 16.66 years, who were diagnosed with chronic graft-versus-host disease, in order to assess the number and progression of dental caries lesions and the presence of dental plaque. Caries risk was assessed using the Cariogram based on data from the clinical examination, general health, and diet questionnaires. Patients completed the Oral Health Impact Profile questionnaire. The scores from each area were summed to determine the Oral Health Impact Profile summary score. Samples of saliva were collected from the same patients, and salivary tests (unstimulated and stimulated salivary flow, pH value of unstimulated and stimulated saliva, buffering capacity of stimulated saliva, colony density of *Lactobacillus* and *Streptococcus mutans* bacteria) were performed. **Results:** Greater psychological discomfort correlated with a lower unstimulated salivary flow rate (R = -0.511, p = 0.0212), a lower pH of stimulated saliva (R = -0.495, p = 0.0266), more tooth sites with cavitated dentin lesions (R = 0.609, p = 0.0034) and fewer teeth (R = -0.599, p = 0.0041). A higher Oral Health Impact Profile summary score correlated with a lower pH of the stimulated saliva (R = -0.486, p = 0.0297), fewer teeth (R = -0.726, p = 0.00019), more tooth sites with cavitated dentin lesions (R = 0.588, p = 0.00509) and a higher caries risk (R = 0.542, p = 0.0112). A poorer assessment of oral health correlated with a higher caries risk (R = 0.512, p = 0.0177). **Conclusions**: In summary, the study showed that patients have lower oral health-related quality of life as a consequence of diminished salivary flow rate therefore elevated caries risk factors and negative effect on oral health.

Keywords: dental caries; oral health related quality of life; xerostomia; bone marrow transplantation; saliva; graft-versus-host disease; haematology; clinical study

1. Introduction

Chronic graft-versus-host disease (cGVHD) is a serious complication following allogeneic haematopoietic stem cell transplantation that affects up to 80% of transplant recipients [1]. It can occur in children with an incidence of 20-40% and in adults with an incidence of around 50%, increasing to 60% with advancing age [2–4]. The disease manifests as a systemic multi-organ disease that typically affects the skin, eyes, mouth, liver, genitals, gastrointestinal tract, lungs and musculoskeletal system [5]. The pathophysiology of cGVHD is complex and not fully understood. It involves donor autoreactive and alloreactive T and B cells that attack host tissues either by a direct response or by severe inflammatory reactions [6]. During treatment with multiple immunosuppressive drugs, the recipient's immune system is no longer able to recognise its own cells,

 doi:10.20944/preprints202501.0698.v1

resulting in clinical features that resemble autoimmune diseases such as scleroderma or Sjögren's syndrome [7–9].

Oral manifestations of cGVHD deserve special attention as the oral cavity is one of the most commonly affected sites and is often the primary site of disease manifestation [19]. Oral cGVHD presents with various clinical features including mucosal changes, taste alterations, restricted tongue mobility, reduced mouth opening, desquamative gingivitis and salivary gland dysfunction with xerostomia or mucocele [8]. The disease leads to destruction of the salivary gland acini and thus to quantitative and qualitative changes in saliva, which are exacerbated by immunosuppressive therapy [10]. The impact on oral health is significant, as reduced salivary flow impairs the oral cavity's immunity to infection and increases susceptibility to mechanical and chemical injury to oral mucosa. Patients also have an increased risk of tooth decay, tooth loss and the need for extensive dental treatment. In addition, these patients have a higher risk of developing oral squamous cell carcinoma [8,11]. The comprehensive care of cGVHD patients requires a multidisciplinary approach involving transplant specialists, dermatologists, ophthalmologists, dentists, and other medical professionals, depending on the organs involved. Long-term follow-up is essential to monitor disease progression, manage complications and adjust treatment strategies if necessary.

Dental caries is a chronic, multifactorial disease characterised by the demineralisation of hard dental tissues by bacterial acids [12]. The process begins as subclinical enamel dissolution, potentially progressing to visible non-cavitated and eventually cavitated lesions. Without treatment, caries can advance to pulp infection, causing inflammation and necrosis [13,14]. Several key factors influence caries development. Saliva provides essential protective mechanisms through surface cleaning, acid buffering, bacterial control, and remineralisation promotion. Reduced salivary flow significantly increases caries risk [15,16]. Dental plaque bacteria, particularly *Streptococcus mutans* and *Lactobacillus*, create acidic conditions that promote tooth demineralisation when pH drops below 5.5 [17–21]. Dietary habits, especially frequent consumption of fermentable carbohydrates, significantly impact caries development [22,23]. Regular exposure to fluoride through various applications enhances tooth resistance to acid dissolution and promotes remineralisation, reducing caries susceptibility by 30-70% [18,24,25].

Determining a patient's likelihood of developing dental caries is essential for creating an effective treatment plan. However, this evaluation presents challenges because tooth decay develops through multiple interacting factors. The assessment needs to consider various personal characteristics that affect the balance between tooth mineral loss and its restoration [24]. The Cariogram software provides an unbiased tool for evaluating caries risk. This freely accessible program calculates the probability of new cavity development by analyzing multiple risk factors, including dietary habits (frequency and quantity of food consumption), bacterial factors (dental plaque levels and *Streptococcus mutans* presence), individual susceptibility (use of fluoride products, saliva's buffering ability, and saliva production rate), and current health status (existing cavities and related health conditions). The main purpose of Cariogram is to identify patients with high cavity risk so that appropriate preventive strategies and causative treatment regimens can be implemented [26].

The Oral Health Impact Profile (OHIP) questionnaire is one of the most widely accepted and comprehensive measures of subjective assessment of oral health-related quality of life, as its questions cover a wide range of areas that influence quality of life [27]. It assesses quality of life from three perspectives: physical, psychological and social [28]. It is one of the most useful tools in oral health research to compare the success of different treatment methods and it has been translated into more than 10 languages. OHIP-49 has been translated also into Slovenian (OHIP-SVN) and is a suitable instrument to assess oral health-related quality of life in Slovenia [27].

The aim of this study was to determine the impact of cGVHD on oral health-related quality of life.

2. Materials and Methods

23 adult patients who had undergone allogeneic haematopoietic stem cell transplantation and were diagnosed with cGVHD (10 men and 13 women) were included in this study. They were between 21 and 67 years old, with an average age of 42.28 ± 16.66 years. They had different primary blood diseases: 15 patients had acute myeloid leukaemia (AML), 6 patients had acute lymphoblastic

 doi:10.20944/preprints202501.0698.v1

leukaemia (ALL), one patient had T cell lymphoma, and one patient had myelodysplastic syndrome. 15 patients suffered from mild cGVHD (grade I), 5 from moderate cGVHD (grade II) and 2 from severe cGVHD (grade III).

All patients were invited during their regular clinical visit at the Department of Haematology of the University Clinical Center Ljubljana and informed about the aim and procedure of the study and received a written explanation. Patients voluntarily and consciously participated in the study. Before the clinical procedures, all patients signed a consent form for the present study. It was approved by the National Medical Ethics Committee of the Republic of Slovenia under the number 0120-539/2016-2 KME 40/11/16.

First, patients completed a questionnaire on general health, oral health and diet. Subsequently, 2 calibrated researchers performed clinical examinations and salivary tests. Carious lesions were evaluated and categorised into non-cavitated lesions, cavitated lesions in enamel and cavitated lesions in dentin. Caries risk factors evaluated were unstimulated and stimulated salivary flow, pH of stimulated and unstimulated saliva, buffering capacity of stimulated saliva and colony density of *Lactobacillus* and *Streptococcus mutans* bacteria. The Cariogram computer programme was used to assess the caries risk.

The OHIP-SVN was used to assess oral health-related quality of life, which participants completed at the end of their clinical examination. The questionnaire assesses categories such as limited functionality, psychological difficulties, physical pain, physical, psychological, social, and general impairment. The questionnaire also assesses the participant's perception of their oral health and appearance. In the questions of the questionnaire, participants are asked to indicate how often they have had certain problems in the last few months. The answers are analysed on a Likert scale: 0 means never, 1 rarely, 2 occasionally, 3 often, 4 always. Zero means that a particular problem is not present, while the highest value indicates a clearly present problem [29]. The values of the individual categories were then added together to obtain the OHIP summary score.

The statistical analysis was carried out using SigmaPlot 14.0 software (Systat). All results are given as arithmetic means (M) with the corresponding standard deviations (SD). The criterion for determining statistical significance was a p-value of less than 0.05.

The linear regression method was used to assess the correlation between the measured parameters (unstimulated and stimulated salivary flow, pH of stimulated and unstimulated saliva, buffer capacity of stimulated saliva and colony density of *Lactobacillus* and *Streptococcus mutans* bacteria, results of the OHIP-SVN questionnaire), using Pearson correlation for parametric variables and Spearman correlation for non-parametric variables.

3. Results

3.1. Results of the OHIP-SVN Questionnaire

The results are shown in Table 1.

Table 1. Results of the OHIP-SVN questionnaire.

Domain	Score (Mean and SD)
Self-assessed oral health	2.21 ± 0.9
Self-assessed oral aesthetic	2.09 ± 0.86
Functional limitation	10.5 ± 7
Physical pain	6.95 ± 4.69
Psychological discomfort	7.09 ± 5.33
Physical disability	7.01 ± 6.93
Psychological disability	3.23 ± 4
Social disability	1.32 ± 2.17
Handicap	2.91 ± 4.15
OHIP summary score	40.81 ± 31.83

 doi:10.20944/preprints202501.0698.v1

3.2. Correlations Between the Measured Parameters and the Results of the OHIP-SVN Questionnaire

The results showed that a poorer assessment of oral health correlated with a higher caries risk (R = 0.512, p = 0.0177). Greater psychological discomfort correlated with lower unstimulated salivary flow (R = -0.511, p = 0.0212), lower pH of stimulated saliva (R = -0.495, p = 0.0266), a greater number of tooth sites with cavitated lesions in dentin (R = 0.609, p = 0.0034), and a lower number of teeth (R = -0.599, p = 0.0041). A higher OHIP summary score correlated with a lower pH of stimulated saliva (R = -0.486, p = 0.0297), a lower number of teeth (R = -0.726, p = 0.00019) and a greater number of tooth sites with cavitated lesions in the dentin (R = 0.588, p = 0.00509). A higher OHIP summary score also correlated with a higher caries risk (R = 0.542, p = 0.0112).

4. Discussion

According to the results obtained in a study by Rener-Sitar et al. involving a population of 400 healthy participants our patients reported a poorer oral health-related quality of life [30]. This was expected, as we found reduced salivary flow in our participants, which negatively affected oral health and, in turn, lowered the quality of life. In comparison to the general population in the mentioned study by Rener-Sitar et al., participants in our study rated their functionality as more limited, experienced more psychological issues, greater physical impairment, higher mental distress, greater social dysfunction, and a higher overall impairment.

CGVHD significantly impacts patients' quality of life across multiple dimensions, making it notably different from the general healthy population [1,31].

Saliva plays a vital role in maintaining oral health through its multiple protective functions. It aids in lubrication, buffering, remineralisation, antimicrobial activity, and facilitates taste perception and digestion. When salivary flow is reduced (hyposalivation), it significantly impacts both oral health and quality of life. Patients with reduced salivary flow often experience xerostomia (dry mouth sensation), difficulties in speaking, eating, and swallowing, and may require frequent water intake. The condition can lead to various oral manifestations including loss of mucosal glossiness, development of thin and cracked oral mucosa, tongue fissures, angular cheilitis, and increased susceptibility to oral infections, particularly candidiasis [32]. Furthermore, reduced salivary flow increases the risk of dental caries, especially in atypical locations, due to decreased buffering capacity and protective properties of saliva. The physical manifestations of cGVHD difficulties often lead to functional limitations in daily activities, causing fatigue and reduced physical capabilities.

Our results correlate with those of Stolze et al., who performed a similar study to ours and assessed the oral health-related quality of life in patients with oral cGVHD [33]. The shorter version of OHIP with 14 questions (OHIP-14) was used and their results showed that oral health-related quality of life was impaired and mostly negatively affected by complaints of oral pain and oral sensitivity and less by the severity of oral mucosal cGVHD.

Psychological recovery after bone marrow transplantation is typically longer than physical recovery, particularly in patients with persistent cGVHD [34,35]. While most transplantation survivors demonstrate high resilience, they face numerous emotional challenges including uncertainty, fear of relapse, anxiety, and depression. Factors associated with increased vulnerability to emotional difficulties include traumatic transplantation experience, lower education levels, lower income, and poorer pre-transplantation mental health [36,37]. Notably, persistent cGVHD and poor current health status correlate with more severe psychological symptoms. Despite these challenges, less than half of survivors with psychological needs receive appropriate treatment [38].

Our study did not find any other statistically significant differences between the severity of cGVHD and different underlying diagnoses, in relation to the quality of life associated with oral health.

Our results showed an association between a lower number of teeth and poorer quality of life related to oral health in patients diagnosed with cGVHD, according to the OHIP questionnaire. Studies have shown that tooth loss disrupts oral function and leads to difficulties in chewing and impaired aesthetics [39]. Poorer quality of life is also linked to a greater number of tooth surfaces with cavitated lesions in the dentin, as found by Leal and colleagues, who investigated the oral health-related quality of life of children with cavitated lesions in the dentin. These lesions cause pain and, due to sensitivity, make chewing with affected teeth more difficult [40].

 doi:10.20944/preprints202501.0698.v1

Psychological issues in our participants, such as worry about teeth, discomfort, feelings of misfortune, and tension related to oral health problems, were statistically significantly associated with salivary parameters that contribute to caries formation and progression and to poorer dental status. Additionally, we found that a poorer self-reported oral health status was linked to a higher risk of developing caries. A higher risk of caries was also associated with poorer quality of life, according to the results from the OHIP questionnaire.

The overall caries risk assessment includes salivary parameters, participants' previous experiences with carious lesions or dental status, plaque on tooth surfaces, diet, fluoride intake, and systemic diseases that directly or indirectly affect the oral condition in patients with chGVHD [26]. High caries risk indicates that individuals have a low chance of avoiding new carious lesions in the future, which would lead to further deterioration of their oral health and quality of life. This situation could be improved through preventive dental visits implemented at the time of primary disease diagnosis and before bone marrow transplantation. By incorporating dental care into the initial treatment planning, healthcare providers could take a more proactive approach to maintaining patients' oral health, potentially reducing complications and improving overall quality of life throughout their medical journey. This is especially important as it's the only way to break the vicious cycle caused by the described dynamics.

Funding: This work was funded by the programme grants of the Slovenian Research Agency, ARRS P3-0019. The funder had no role in the design, data collection, data analysis, or reporting of this study.

Institutional Review Board Statement: Prior to the clinical procedures, all patients signed an informed consent form for the present study. It was approved by the National Medical Ethics Committee of the Republic of Slovenia - number 0120-539/2016-2 KME 40/11/16.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The complete data will be sent on request.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Baird K, Pavletic SZ. Chronic graft versus host disease. Curr Opin Hematol. 2006;13(6):426–35.
2. Grube M, Holler E, Weber D, Holler B, Herr W, Wolff D. Risk Factors and Outcome of Chronic Graft-versus-Host Disease after Allogeneic Stem Cell Transplantation—Results from a Single-Center Observational Study. Biol Blood Marrow Transplant. 2016;22(10):1781–91.
3. Arai S, Arora M, Wang T, Spellman SR, He W, Couriel DR, et al. Increasing Incidence of Chronic Graft-versus-Host Disease in Allogeneic Transplantation – A Report from CIBMTR. Biol Blood Marrow Transplant. 2015;21(2):266–74.
4. Baird K, Cooke K, Schultz KR. Chronic Graft-Versus-Host Disease (GVHD) in children. Pediatr Clin North Am. 2010;57(1):297–322.
5. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945–56.
6. Cooke KR, Luznik L, Sarantopoulos S, Hakim F, Jagasia M, Fowler D, et al. The Biology of Chronic Graft-versus-Host Disease: A Task Force Report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease. Biol Blood Marrow Transplant. 2017;23(2):211–34.
7. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2015;21(3):389–401.
8. Meier JKH, Wolff D, Pavletic S, Greinix H, Gosau M, Bertz H, et al. Oral chronic graft-versus-host disease: Report from the International Consensus Conference on clinical practice in cGVHD. Vol. 15, Clinical Oral Investigations. 2011. p. 127–39.
9. Lee SJ, Vogelsang G, Flowers MED. Chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2003;9(4):215–33.

 doi:10.20944/preprints202501.0698.v1

10. Imanguli MM, Atkinson JC, Mitchell SA, Avila DN, Bishop RJ, Cowen EW, et al. Salivary Gland Involvement in Chronic Graft-Versus-Host Disease: Prevalence, Clinical Significance, and Recommendations for Evaluation. Biol Blood Marrow Transplant. 2010;16(10):1362–1369.
11. Treister N, Duncan C, Cutler C, Lehmann L. How we treat oral chronic graft-versus-host disease. Blood. 2012;120(17):3407–18.
12. Featherstone JDB. The science and practice of caries prevention. J Am Dent Assoc. 2000;131(7):887–99.
13. Pretty IA, Ekstrand KR. Detection and monitoring of early caries lesions: a review. Eur Arch Paediatr Dent. 2016;17(1):13–25.
14. Nyvad B, Fejerskov O. Assessing the stage of caries lesion activity on the basis of clinical and microbiological examination. Community Dent Oral Epidemiol. 1997;
15. Humphrey SP, Williamson RT. A review of saliva: Normal composition, flow, and function. J Prosthet Dent. 2001;85(2):162–9.
16. Scully C, Felix DH. Oral Medicine — Update for the dental practitioner. Dry mouth and disorders of salivation. Br Dent J. 2005;199(7):423–7.
17. Marsh PD. Dental plaque as a biofilm and a microbial community - Implications for health and disease. BMC Oral Health. 2006;6(Suppl 1).
18. Rodrigues JA, Lussi A, Seemann R, Neuhaus KW. Prevention of crown and root caries in adults. Periodontol 2000. 2011;55(1):231–49.
19. Seneviratne CJ, Zhang CF, Samaranayake LP. Dental plaque biofilm in oral health and disease. Chinese J Dent Res. 2011;14(2):87–94.
20. Struzycka I. The Oral Microbiome in Dental Caries. Polish J Microbiol. 2014;63(2):127–35.
21. Tanzer JM, Livingston J, Thompson AM. The Microbiology of Primary Dental Caries in Humans. J Dent Educ. 2001;65(10):1028–37.
22. Lingstrom P, Birkhed D, Ruben J, Arends J. Effect of Frequent Consumption of Starchy Food Items on Enamel and Dentin Demineralization and on Plaque pH in situ. J Dent Res. 1994;73(3):652–60.
23. Rugg-Gunn A. Dental caries: strategies to control this preventable disease. Acta Med Acad. 2013;42(2):117–30.
24. Featherstone JDB. The continuum of dental caries - Evidence for a dynamic disease process. J Dent Res. 2004;83(Spec Iss C):C39–42.
25. Cury JA, Tenuta LM. How to maintain a cariostatic fluoride concentration in the oral environment. Adv Dent Res. 2008;20(1):13–6.
26. Bratthall D, Petersson GH. Cariogram - A multifactorial risk assessment model for a multifactorial disease. Community Dent Oral Epidemiol. 2005;33(4):256–64.
27. Rener-Sitar K, Celebić A, Petricević N, Papić M, Sapundzhiev D, Kansky A, et al. The Slovenian version of the Oral Health Impact Profile Questionnaire (OHIP-SVN): translation and psychometric properties. Coll Antropol. 2009;33(4):1177–83.
28. Zucoloto ML, Maroco J, Campos JADB. Impact of oral health on health-related quality of life: A cross-sectional study. BMC Oral Health. 2016;16(1):2–7.
29. Rener-sitar K, Petričević N, Čelebić A, Marion L. Psychometric Properties of Croatian and Slovenian Short Form of Oral Health Impact Profile Questionnaires. Croat Med J. 2008;49:536–44.
30. Rener-Sitar K, Čelebić A, Stipetić J, Marion L, Petričević N, Zaletel-Kragelj L. Oral health related quality of life in Slovenian patients with craniomandibular disorders. Coll Antropol. 2008;32(2):513–7.
31. Lee SJ, Kim HT, Ho VT, Cutler C, Alyea EP, Soiffer RJ, et al. Quality of life associated with acute and chronic graft-versus-host disease. Bone Marrow Transplant. 2006;38(4):305–10.
32. Epstein JB, Scully C. The role of saliva in oral health and the causes and effects of xerostomia. J Can Dent Assoc. 1992;58(3):217–21.
33. Stolze J, Boor M, Hazenberg MD, Brand HS, Raber-Durlacher JE, Laheij AMGA. Oral health–related quality of life of patients with oral chronic graft-versus-host disease. Support Care Cancer. 2021;29(11):6353–60.
34. Bishop MM. Psychosocial Sequelae of Hematopoietic Cell Transplantation in Survivors and Caregivers. Biol Blood Marrow Transplant. 2009;15(1 SUPPL.):29–32.

 doi:10.20944/preprints202501.0698.v1

35. Syrjala KL, Langer SL, Abrams JR, Storer B, Sanders JE, Flowers MED, et al. Recovery and long-term function after hematopoietic cell transplantation for leukemia or lymphoma. Jama. 2004;291(19):2335–43.
36. Wong FL, Francisco L, Togawa K, Bosworth A, Gonzales M, Hanby C, et al. Long-term recovery after hematopoietic cell transplantation: Predictors of quality-of-life concerns. Blood. 2010;115(12):2508–19.
37. Wingard JR, Huang IC, Sobocinski KA, Andrykowski MA, Cella D, Rizzo JD, et al. Factors Associated with Self-Reported Physical and Mental Health after Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2010;16(12):1682–92.
38. Mosher CE, Duhamel KN, Rini CM, Li Y, Isola L, Labay L, et al. Barriers to mental health service use among hematopoietic SCT survivors. Bone Marrow Transplant. 2010;45(3):570–9.
39. Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NHJ. Tooth loss and oral health-related quality of life: A systematic review and meta-analysis. Health Qual Life Outcomes. 2010;8(1):126.
40. Leal SC, Bronkhorst EM, Fan M, Frencken JE. Untreated cavitated dentine lesions: Impact on children's quality of life. Caries Res. 2012;46(2):102–6.