Received: 3 May 2019 | Revised: 14 June 2019 | Accepted: 17 June 2019

DOI: 10.1111/ejh.13283

ORIGINAL ARTICLE

European Journal of Haematology WILEY

Common oral diseases, hyposalivation and survival post-HSCT, a longitudinal study

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Abstract

Objectives: Haematopoietic stem cell transplantation (HSCT) recipients are at risk of side effects within the oral cavity. The purpose of this study was to examine progression of common oral diseases and hyposalivation and their associations with survival in allogeneic HSCT recipients.

Methods: Two hundred and sixty nine adult HSCT recipients treated with HSCT between 2008 and 2016 were included in this study. The associations of caries, decayed, missing, filled teeth (DMFT) index, radiological attachment loss and stimulated salivary flow rate with 6-month survival and the progression of the oral disorders within 2 years were examined.

Results: Forty HSCT recipients (14.8%) deceased within 6 months post-HSCT. Among the deceased recipients, hyposalivation and caries were more common pre-HSCT than in recipients who survived over 6 months ($P < 0.05$). HSCT recipients with hyposalivation pre-HSCT had higher risk of death (HR: 1.90, 95% CI:1.00-3.60; $P = 0.044$) within 6 months post-HSCT compared with recipients without hyposalivation. Hyposalivation pre-HSCT was associated with a higher DMFT index score ($P < 0.05$) and a smaller number of teeth ($P < 0.005$) 24 months post-HSCT in comparison with those without hyposalivation.

Conclusions: Hyposalivation and caries were associated with a lower rate of survival in HSCT recipients. Additionally, hyposalivation predisposed to deterioration of oral health post-HSCT.

KEYWORDS

dental caries, dmf index, graft vs host disease, haematology, hyposalivation, stem cell transplantation

1 | INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is a treatment used for patients with life-threatening diseases and disorders of the haematopoietic system. In HSCT, haematopoietic multipotent stem cells are collected either from a donor (allogeneic-HSCT) or the patient him/herself (autologous-HSCT). Before transplantation, intense conditioning regimen including high-dose chemotherapy and for some indications, total body irradiation (TBI) is used to eradicate patients' own haematopoietic stem cells.[1-3] Subsequent to improvements of the transplantation procedures, the number of long-term survivors has increased and the

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prevalence of life-threatening complications has decreased over the years.[3-7] However, less severe side effects are still common and can affect nearly all organs.[3,4,7] HSCT recipients are predisposed to infectious diseases, and the quality of life can be reduced throughout the lifetime.[4,7-10] Thus, prevention and treatment of these comorbidities are of increasing clinical importance and essential for supportive care.

Side effects and disorders of the oral cavity are common and can be found in approximately 80% of the HSCT recipients. Of these, hyposalivation is particularly frequent and may be one of the fundamental factors in the pathogenesis of oral disorders post-HSCT.[8-14] Over time, hyposalivation and changes in salivary composition and oral biofilms almost inevitably cause dental caries, periodontitis and mucosal infections.[13-16] Additionally, hyposalivation and xerostomia (subjective sensation of dry mouth) can lead to oral discomfort, may affect the patient's ability to eat and cause increased need of supportive cancer care.[8,13,14,16,17] Hyposalivation is associated with oral GvHD and mucositis and could thus even be associated with survival.[12,18-22] Among HSCT recipients, this has not been studied, but hyposalivation and associated saliva alterations have been observed to co-exist with aspiration pneumonia as well as frailty and death among elderly.[23-26]

Reasons for hyposalivation in HSCT recipients are likely multifactorial. The conditioning regimen before HSCT can potentially affect salivary glands, particularly if TBI is used.[3,27] Additionally, salivary glands are commonly affected by Graft vs Host Disease (GvHD). In GvHD, the infiltrating T- lymphocytes cause cytotoxicity in the salivary glands and reduce the secretion of saliva.[19-22] Furthermore, HSCT recipients often need a broad range of medications, most of which might reduce saliva secretion.[13] However, in our previous study, use of medications could not explain hyposalivation in HSCT recipients.[27,28]

Several current guidelines support dental screening and elimination of potential oral foci before HSCT as the HSCT treatment includes strong immunosuppression predisposing recipients to severe infection complications.[3,9,11,29] It has been estimated that 1.8 of every 1000 deaths could be prevented with dental treatment before HSCT.[30] However, the recommendations are somewhat inconsistent and based on a limited number of studies, some of which have shown that chronic oral foci including deep caries are not associated neither with survival nor infection complications.[31,32] Nonetheless, several studies have confirmed relationship between periodontal bacteria and oral mucositis and that the treatment of periodontitis can reduce oral comorbidities, in terms of mucositis post-HSCT, and thus, enhance healing of the recipients.[33,34]

Only a few studies exist on the oral health of adult subjects pre- and post-HSCT. These studies suggest hyposalivation to be common and oral health to deteriorate after the HSCT.[8,12,15,27,35,36] Additionally, there are no studies on the effects of hyposalivation or the most common oral infections caries and periodontitis on survival post-HSCT. Thus, in this study, the prevalence, consequences and progression of caries and periodontitis, as well as hyposalivation were examined in a considerably large number of allogeneic HSCT recipients pre- and up to 24 months post-HSCT.

2 | PATIENTS AND METHODS

This retrospective observational longitudinal study was performed according to the Declaration of Helsinki and was approved by ethics committee (Ethikkommision Nordwest- und Zentralschweiz (EKNZ), Switzerland: EKNZ: 311-10).

Adult allogeneic HSCT recipients who were treated for haematological malignancies in the Department of Hematology, University Hospital Basel, Switzerland, between 2008 and 2016 with complete medical and oral health status were included. HSCT recipients whose Stimulated salivary flow rate (SSFR) was not measured, panoramic radiography was not taken pre-HSCT or who were edentulous were excluded. Before oral examination, most HSCT recipients had received conditioning chemotherapy either with or without TBI as previously described.[28,37] Diagnosis, conditioning-related information, survival as well as the presence and grade of acute GvHD (aGvHD) according to the modified Glucksberg criteria by Przepiorka et al (1995) (symptoms starting <100 days post-HSCT) and presence and grade of chronic GvHD (cGvHD) according to Filipovich et al (2005) were collected from the medical records.[38-40]

Clinical and radiological oral and dental examinations were carried out by experienced dentists in the Department of Oral Health & Medicine (previous Department of Preventive Dentistry and Oral Microbiology), University Center for Dental Medicine Basel, University of Basel. The first oral examination took place prior to HSCT following the normal routine protocol of the clinic always including a panoramic radiograph, SSFR measurements and clinical diagnostics and post-HSCT also observation of oral manifestations of GvHD (yes/no). All HSCT recipients participated in a prospective oral disease prevention programme. Oral hygiene instruction was provided, daily use of fluoride containing mouth rinses and toothpaste as well as saliva substitutes and chlorhexidine-containing mouth rinse were recommended for HSCT recipients in aplasia.[11] Follow-up examinations were performed 6, 12 and 24 months post-HSCT.

Stimulated salivary flow rate measurement was conducted at each appointment as described in our previous studies.[28,41] SSFR ≤ 0.7 mL/min was defined as hyposalivation, and SSFR ≤ 0.3 mL/min as severe hyposalivation.[13] Oral and dental examination, including decayed, missing, filled teeth (DMFT) index according to WHO, was performed.[42] Current or already treated periodontitis was assessed from panoramic radiographs. Periodontitis was determined to be present if radiological attachment loss (RAL), for example the distance between the cementoenamel junction and the alveolar bone crest, was observed to be >3 mm.[43]

2.1 | Statistics

Mean, median and standard deviation of the oral health parameters including SSFR, DMFT index, number of teeth, number of caries lesions and the frequency of periodontitis were calculated and put in relation to SSFR (hyposalivation vs normal SSFR). Descriptive univariate analyses were done by sex (male vs female)

TABLE 1 Descriptives of the study subjects (269)

Age, mean (range)	50.6 (19-74)
Sex n (%)	
Female	127 (47.2)
Male	142 (52.8)
Diagnosis n (%)	
AML	89 (33.1)
MDS	28 (10.4)
ALL	37 (13.8)
CML	9 (3.3)
CLL	16 (5.9)
PCD	28 (10.4)
BMF	7 (2.6)
MPN	21 (7.8)
MH	3 (1.1)
NHL	27 (10.0)
Other	4 (1.5)
Karnofsky, mean (range)	91.1 (40-100)
Ablative conditioning n (%)	
Yes	218 (81.0)
No	51 (19.0)
TBI n (%)	
Yes	110 (40.9)
No	150 (55.8)
n.app	9 (3.3)

Abbreviations: ALL, Acute Lymphoblastic Leukaemia; AML, Acute Myeloid Leukaemia; BMF, Bone Marrow Failure; CLL, Chronic Lymphocytic Leukaemia; CML, Chronic Myeloid Leukaemia; MDS, Myelodysplastic Syndrome; MH, Hodgkin's Lymphoma; MPN, Myeloproliferative Neoplasm; NHL, Non-Hodgkin's-Lymphoma; PCD, Plasma Cell Dyscrasia; TBI, Total Body Irradiation.

and by survival status (survived vs deceased). ANOVA was used to determine the association of SSFR with presence and grade of cGvHD and univariate analyses to determine the association of SSFR with presence of oral manifestations of GvHD. Pearson Chi-square, *t* test and Mann-Whitney *U* test were used to determine statistical significance. *P*-value of < 0.05 was considered as statistically significant. For the survival analysis, Cox proportional hazards regression models were used to analyse the 6-month survival of HSCT recipients with and without hyposalivation pre-HSCT. Statistical analyses were performed with IBM SPSS software, version 23 (IBM Corporation, Amonk).

3 | RESULTS

3.1 | Study population

A total of 269 adult allogeneic HSCT recipients (m/f: 142/127; age mean: 50.6 years; range 19-74 years) were included. Excluded were 73 allogeneic HSCT recipients whose dental or medical data were not complete. 155 (57.6%) recipients had received the diagnosis within 1 year of the pre-HSCT dental examination, 69 (25.7%) recipients between one to 5 years and 45 (16.7%) more than 5 years prior to HSCT. Descriptive data and diagnoses are presented in Table 1. In the follow-up examinations 140, 106 and 49 individuals participated at 6, 12 and 24 months post-HSCT, respectively. During the study period, 101 HSCT recipients were deceased.

The mean SSFR in all HSCT recipients pre-HSCT was 1.13 (± 0.72) mL/min. In 15 (5.6%) HSCT recipients pre-HSCT, the SSFR was <0.3 mL/min, 76 (28.3%) 0.3-0.7 mL/min and >0.7 mL/min in 178 (66.2%). The mean DMFT index score was 18.9 (±7.7), mean number of teeth 24.7 (± 6.7), mean number of caries lesions 1.0 (± 2.2) and the prevalence of periodontitis (RAL > 3 mm) 65.1%.

3.2 | Associations of SSFR and oral disorders with survival post-HSCT

Forty HSCT recipients (14.8%) deceased during the first 6 months post-HSCT. There was no statistically significant difference in age (mean age 49.5 years vs 50.8 years) or sex (male 52.5% vs female 52.8%) between the deceased and the survivors after 6 months post-HSCT. Hyposalivation (SSFR ≤ 0.7 mL/min) pre-HSCT was more common among the deceased compared with the survivors (47.5% vs 31.4%; $P = 0.048$). Also, caries incidence was higher among the deceased compared with the survivors within 6 months post-HSCT (mean 2.0 ± 3.0 vs 0.88 ± 2.0; $P = 0.044$). There were no statistically significant differences in mean DMFT index, the number of teeth or the presence of periodontitis (RAL > 3 mm) between the deceased and the survivors within 6 months post-HSCT (Table 2).

In the survival analysis, HSCT recipients who had hyposalivation (SSFR ≤ 0.7 mL/min) pre-HSCT had a higher risk of death 6 months post-HSCT. The age- and sex-adjusted hazard ratio of dying within 6 months post-HSCT was almost twice as high in the hyposalivation group, HR: 1.90 (95% CI: 1.00-3.60; $P = 0.044$), compared with the reference group which consisted of HSCT recipients without hyposalivation pre-HSCT.

3.3 | Stimulated saliva flow rates and associations of hyposalivation with DMFT index, caries, number of teeth and GVHD post-HSCT

Stimulated salivary flow rate 6 months post-HSCT was lower (mean: 0.93 ± 0.6 mL/min) compared with SSFR pre-HSCT (1.13 ± 0.73 mL/min; $P = 0.009$). However, after a year the SSFR returned to the initial level (1.13 ± 0.63 mL/min) and 2 years post-HSCT above the initial level (1.27 ± 0.75 mL/min).

There was no statistically significant difference in mean DMFT index between HSCT recipients with hyposalivation pre-HSCT and recipients with normal SSFR pre-HSCT or 6 and 12 months post-HSCT. 24 months post-HSCT, the mean DMFT index in HSCT recipients with hyposalivation pre-HSCT was higher compared with HSCT recipients with normal SSFR (23.55 ± 5.61 vs 17.95 ± 7.07; $P = 0.02$; Table 3). The results on the number of teeth were in line with those

TABLE 2 Comparison of survival and pre-HSCT oral health parameters

	Survival ≤ 6 mo (40)	Survival > 6 mo (229)	*P*-value
SSFR mL/min mean (±SD)	0.98 (0.7)	1.15 (0.7)	
SSFR ≤ 0.7 mL/min (n; %)	19 (47.5)	72 (31.4)	0.048
Number of caries mean (±SD)	2.0 (3.0)	0.9 (2.0)	0.044
Number of teeth mean (±SD)	24.1 (6.5)	24.8 (6.8)	
DMFT index mean (±SD)	18.5 (8.7)	18.9 (7.5)	
RAL> 3 mm (%)	22 (55.0)	153 (66.8)	

Abbreviations: DMFT index, Decayed Missing Filled Teeth index; RAL, Radiological Attachment Loss; SSFR, Simulated Salivary Flow Rate.

on DMFT index, as 24 months post-HSCT, the HSCT recipients with hyposalivation had a lower number of teeth compared with HSCT recipients with normal SSFR (mean 20.7 ± 7.6 vs 27.0 ± 4.9; $P = 0.001$).

Caries was consistently more prevalent pre-HSCT and 6, 12 and 24 months post-HSCT in HSCT recipients with hyposalivation but the differences were not statistically significant, except for caries prevalence pre-HSCT (mean caries in HSCT recipients with hyposalivation vs normal SSFR pre-HSCT: 1.45 ± 2.4 vs 0.84 ± 2.0; $P = 0.04$, respectively).

There was no statistically significant difference in aGvHD (no vs yes and/or according to grade I-IV) post-HSCT between HSCT recipients with hyposalivation pre-HSCT and recipients with normal SSFR pre-HSCT. Additionally, hyposalivation pre-HSCT was not associated with cGvHD (mild, moderate or severe cGvHD). However, mean SSFR of patients suffering from severe cGvHD was lower when compared to the patients with limited or no cGvHD post-HSCT but the differences were not statistically significant. The mean SSFR of patients with severe cGvHD did not return to the initial level 24 months post-HSCT rather stayed at the same level as 1 year post-HSCT (1.04 mL/min). Six months post-HSCT, the presence of oral manifestation of GvHD was noted in 64 (23.6%) and 12 months post-HSCT in 44 (16.2%) HSCT recipients. Hyposalivation post-HSCT (6 and 12 months) was not statistically significantly associated with the presence of oral manifestation of GvHD.

4 | DISCUSSION

The present study examined oral health and changes in oral health parameters during a 2-year follow-up in a large number of HSCT recipients. The novel findings of this study were that hyposalivation and caries were associated with an increased risk of death within 6 months post-HSCT. Age, sex, conditioning type and intensity were not associated with survival. The age- and sex-adjusted hazard ratio (HR) of dying within 6 months post-HSCT was almost twice as high in the hyposalivation group when compared to the group consisting of HSCT recipients without hyposalivation pre-HSCT. These results are in line with previous studies, showing associations between hyposalivation, frailty and mortality. However, these studies were performed among older people with a different medical background. [23-25] Nonetheless, some of the HSCT-recipients also suffer from similar clinical appearance of cachexia and frailty as elderly who commonly suffer from hyposalivation.[24] The possible use of SSFR as a predictor for higher risk of death needs further investigation.

Decreased SSFR rates were common already pre-HSCT. Before the transplantation, 15 (5.6%) HSCT recipients had very low SSFR (<0.3 mL/min), 76 (28.3%) 0.3-0.7 mL/min and 178 (66.2%) >0.7 mL/min. After the transplantation, the SSFR was observed to reduce further, being clearly lower 6 months post-HSCT compared with SSFR pre-HSCT. After that, a gradual improvement of SSFR was observed and 12 months post-HSCT, SSFR was at the level of pre-HSCT values and even slightly higher 24 months post-HSCT (Table 3). This commonly observed hyposalivation and gradual improvement of SSFR over time after HSCT is in line with previous studies and further supports the findings which have shown cytotoxic effects of chemotherapy and irradiation to damage salivary glands. Apocrine functions then regenerate gradually during years.[16,17,19,27,28] However, in this study the SSFR of HSCT recipients with severe cGVHD did not return back to the initial level within the 24 months. This situation is also observed in previous studies, in which malfunctions of salivary glands have been reported in patients with cGvHD.[19-21] Nonetheless, this study also suggests that the higher risk of death in the HSCT recipients with hyposalivation may actually explain some of this improvement observed, as hyposalivation (SSFR ≤ 0.7 mL/min) pre-HSCT was significantly more common among the deceased, compared with the survivors. Thus, the former studies may exaggerate the regeneration potential of salivary tissues.[16,17,27,28] Nonetheless, in our previous study, hyposalivation and persisting sicca symptoms were observed to be relatively common several years post-HSCT.[8]

Hyposalivation was not associated with acute or chronic GvHD or oral manifestation of GvHD. In some of the previous studies, cGvHD has been found to affect salivary glands and lead to salivary dysfunction after the onset of GvHD.[20,21,44] However, within the limits of this study, hyposalivation pre-HSCT seems not to have a causative role in the pathogenesis of any form of GvHD. Supporting this assumption, also in a study by Boer et al (2015), no statistically significant differences in salivary flow rates could be found in HSCT recipients at the time of oral GVHD onset.[15] Thus, further prospective clinical studies are necessary to clarify this issue.

TABLE 3 Oral health parameters compared with SSFR

Oral examination time point	SSFR mL/min (±SD) all	N (SSFR ≤0.7 mL/min/>0.7 mL/min)	Number of caries lesions (±SD)		
			SSFR ≤0.7 mL/min	SSFR >0.7 mL/min	*P*-value
Pre-HSCT	1.1 (0.7)	91/178	1.5 (2.4)	0.8 (2.0)	0.04
6 mo post-HSCT	0.9 (0.6)	42/98	2.3 (3.6)	1.6 (2.8)	0.56
12 mo post-HSCT	1.1 (0.6)	32/74	1.8 (3.1)	1.3 (2.2)	0.22
24 mo post-HSCT	1.3 (0.8)	11/38	2.6 (3.5)	0.7 (1.1)	0.13

Abbreviations: DMFT index, Decayed Missing Filled Teeth index; SSFR, Stimulated Salivary Flow Rate.

In the current study, DMFT index was used to determine past and present cariological infections in HSCT recipients. An earlier study with only 36 HSCT recipients has reported a statistically significant increase in DMFT index score already 6 months post-HSCT.[35] Our study cannot thoroughly confirm this previous finding. Likewise, a couple of studies with a 100-day follow-up did not notice any changes in DMFT index or an increase in new dental caries lesions in this short follow-up period.[15,36] However, in this study, hyposalivation was observed to be associated with progression towards a higher DMFT index score. 24 months post-HSCT, the DMFT index score was statistically significantly higher in HSCT recipients with hyposalivation, compared with the HSCT recipients with normal SSFR. The results on the number of teeth were in line with those on DMFT index. 24 months post-HSCT, HSCT recipients with hyposalivation had a significantly lower number of teeth compared with HSCT recipients with normal SSFR. These findings support our hypotheses and many previous studies where hyposalivation has been observed as a risk factor for oral diseases that may eventually lead to tooth loss and expensive oral rehabilitation. Additionally, caries prevalence was observed to be consistently higher in HSCT recipients with hyposalivation at all study time points, but the results were not statistically significant, except for HSCT recipients with hyposalivation pre-HSCT. However, it must be noted that our results may underestimate the cariological problems in HSCT recipients post-HSCT. All the HSCT recipients in the study were referred to a prospective oral disease prevention programme including oral healthcare instruction, as these preventive measures are expected to prevent caries and reduce the effects of hyposalivation.[9,11,13,14]

Ongoing or treated periodontitis in HSCT recipients was determined by measuring RAL from panoramic radiographs. With this method, the prevalence of current or treated periodontitis in this study population was 65%. There is recent evidence on the association of periodontitis with overall cancer mortality.[45] However, previous results of studies of periodontitis' associations with serious infectious complications, like septicaemia, in adults with leukaemia are contradictory.[46,47] In our study, the prevalence of periodontitis pre-HSCT in HSCT recipients who deceased within 6 months post-HSCT was slightly higher in comparison with survivors, but the difference was not statistically significant. It should be noted that the method of determining the presence of periodontitis is inaccurate and can lead to underestimation of the effect of periodontitis on post-HSCT comorbidity and survival, and these results must be observed with caution. This RAL based manner, used also in our previous study, was used to keep the dental visits as short as possible and to avoid bacteraemia and infectious complications prior to the HSCT.[41]

Some of the HSCT recipients have received therapies for their underlying diseases already for years, which could have influenced the oral health pre-HSCT. However, when divided into groups according to time from diagnosis (under 1 year, 1-5 years, over 5 years), there were no statistically significant differences between these groups in the oral health parameters (results not shown). However, a study by Busjan et al (2017) with a limited number of patients with newly diagnosed acute leukaemia had poorer oral health parameters already prior to any treatments when compared with healthy controls.[48] Based on the current and previous studies the diagnosis and preceding therapies cannot completely explain the poor oral health but warrant further studies.

In this study, a considerable loss in the study population was observed. 269 HSCT recipients were included in the study pre-HSCT. However, only 158 HSCT recipients were examined 6 months post-HSCT, 116 participated 1 year post-HSCT and only 57 HSCT recipients 2 years post-HSCT. 101 HSCT recipients deceased during the observation period. Thus, mortality explains only a part of the loss in HSCT recipients. HSCT recipients are referred to University Hospital Basel for HSCT from different centres located at some distance. Many HSCT recipients had difficulties to travel to Basel and had a dentist in their home district, so follow-up was not done in our department. The loss in the study population may cause bias in the results, but the authors feel that this does not skew the primary outcomes.

In conclusion, hyposalivation and caries were associated with a lower rate of survival within 6 months post-HSCT. Further studies are needed to confirm this finding. Additionally, hyposalivation pre-HSCT was associated with an increased DMFT score and a lower number of teeth 2 years post-HSCT. The use of SSFR measurement as a cheap and easy predictor for higher risk of oral comorbidity can be recommended.

CONFLICT OF INTEREST

The authors state no conflict of interest.

Number of teeth (±SD)			DMFT index (±SD)		
SSFR ≤0.7 mL/min	SSFR >0.7 mL/min	*P*-value	SSFR ≤0.7 mL/min	SSFR >0.7 mL/min	*P*-value
23.9 (7.4)	25.2 (6.4)	0.26	19.0 (7.6)	18.8 (7.8)	0.81
23.9 (8.0)	26.1 (5.2)	0.17	19.4 (7.5)	18.6 (7.6)	0.55
24.3 (7.7)	25.5 (5.8)	0.71	18.2 (8.1)	18.9 (6.9)	0.67
20.7 (7.6)	27.0 (4.9)	0.001	23.5 (5.6)	17.9 (7.1)	0.02

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How to cite this article: Uutela P, Passweg J, Halter J, et al. Common oral diseases, hyposalivation and survival post-HSCT, a longitudinal study. *Eur J Haematol*. 2019;103:300–306. https://doi.org/10.1111/ejh.13283