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ORIGINAL ARTICLE

Sicca symptoms and their impact on quality of life among very long-term survivors after hematopoietic SCT

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The objective of this prospective cross-sectional case-control study was to examine the prevalence of dryness symptoms and its impact on quality of life (QoL) among very long-term survivors after hematopoietic SCT (HSCT) in comparison with their respective sibling donors. Forty-four allogeneic HSCT recipients with a long-term survival (median: 17.5; range: 11–26 years) were included. Their respective, HLA-identical sibling donors served as controls. Clinical examinations included saliva flow rates (SFR) and the Schirmer's test. The presence of sicca symptoms of mouth, eyes and skin were inquired. The social functioning (SF)-36 questionnaire was applied. Recipients had lower ($P<0.01$) unstimulated and stimulated mean SFR than donors. Schirmer's test results <5 mm was found in 45% of the recipients in comparison with 27% of the donors ($P=0.07$). Xerostomia (34 *vs* 4 subjects), xerophtalmia (23 *vs* 3) and dry skin (32 *vs* 12) were reported more often by the recipients than donors ($P<0.001$). Sicca symptoms and their objective findings correlated with QoL. The mean SF-36 scores of the donors were significantly higher than those of the recipients for physical component summary. In conclusion, sicca symptoms are common amongst long-term survivors of HSCT and affect remarkably the QoL.

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INTRODUCTION

Allogeneic hematopoietic SCT (HSCT) is a widely used potentially curative treatment for severe hematological diseases. Due to improvement of the transplant procedure and increase of the number of transplantations performed, the number of long-term survivors is constantly increasing.[1–3] Allogeneic HSCT remains nevertheless associated with considerable acute and long-term comorbidities, such as GVHD, organ dysfunction and secondary malignancies. Due to improved survival, a number of less severe symptoms and late effects are of increasing importance; thus sicca symptoms arise as a relevant issue potentially harmful for the quality of life (QoL) of the long-term survivors.

Keratoconjunctivitis sicca that is, dry inflammation of cornea and conjunctiva, and the sicca syndrome that is, generalized dryness including dryness of the oral cavity, eyes and skin are subjectively distressing and clinically challenging conditions. As saliva and tear fluid have lubricating and protective functions, reduced flow rates lead to remarkably increased risk of oral and eye infections, including generalized dental caries, periodontitis, fungal infections and conjunctivitis.[4–7] In addition, subjective symptoms of dry mouth (xerostomia), altered taste/vision, eating and speaking problems and sensation of a foreign body in the eye are common and known to have a significant impact on the QoL.[8] In a recent study, objectively determined hyposalivation was found in $\sim$50% of patients 6 months post-HSCT.[9] In most cases, stimulated saliva flow returned to normal levels within 2 years, but some patients suffered from persisting hyposalivation. Another recent study by Hull *et al.*[10] reported comparable salivary gland hypofunction and xerostomia 6 to 24 months post-HSCT. Moreover, 21% of the subjects were affected by oral mucosal changes consistent with chronic GVHD (cGVHD) and coexisting with cutaneous, hepatic or ocular cGVHD. GVHD is a common complication of HSCT that can directly compromise salivary gland and lacrimal functions.[11–13]

The occurrence of keratoconjunctivitis sicca has been shown to vary between 38 and 10% in HSCT recipients with and without cGVHD, respectively.[7] In addition to GVHD, HSCT may cause other long-term comorbidities, in particular infections, which may require a broad repertoire of therapeutic agents.[14–16] Immunosuppressive agents, corticosteroids and systemic antibiotics may contribute to hyposalivation and eye dryness.[6,17] Moreover, general malnutrition and even vitamin A deficiency can be encountered, causing dehydration with oral and ophthalmological symptoms.[11,18,19]

So far only a few studies have addressed the functional well-being of survivors after HSCT. In a retrospective multicenter analysis in patients surviving 5 years or more after HSCT, a Karnofsky score $\geqslant$90% was reported in 93% and only 6% of these patients did not return to school or work after HSCT.[20] These results were confirmed by another study.[21] In a more recent analysis on the functional status, of patients showed significantly more difficulties in integration back into society after HSCT, in holding down employment or in obtaining or retaining health insurance when compared with their siblings.[2]

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Sicca syndrome could be one of the reasons for the reduced QoL. This has been shown for example, for patients with Sjögren's syndrome, a disease with the predominant finding of oral and ocular sicca symptoms.[22] Data on the occurrence of sicca syndrome and the impact on QoL among long-term survivors after allogeneic HSCT is scarce. We therefore aimed in this study to examine the prevalence of sicca syndrome in long-term survivors of HSCT and to assess its impact on QoL, compared with their HLA-identical sibling donors.

SUBJECTS AND METHODS

In this prospective case-control cross-sectional study, 44 long-term survivors (median: 17.5 years; range: 11–26 years) of allogeneic HSCT treated for their hematological malignancies in the University Hospital of Basel, Switzerland, and their HLA-identical sibling stem cell donors were included. This study is part of a larger study on long-term survivors compared with their respective sibling donors.[23–25] The Ethics Committee of Basel approved the study and an informed consent was obtained from each subject. All recipients received BM as stem cell source, and TBI was part of the conditioning in 39 patients (89%); 28 fractionated and 11 non-fractionated (72% and 28%, respectively). The median age was 41 years (range 5–50 years) for the recipients and 41 years for the donors (3–45 years). There were slightly more male recipients (55%) and slightly more female donors (55%). Acute GVHD was observed in 31 (70%) and cGVHD in 22 (50%) recipients. Nine (20%) patients had extensive cGVHD and 13 (30%) limited cGVHD. At the time of the evaluation eight patients were still diagnosed with active cGVHD (five extensive, three limited form). Primary diagnoses and characteristics of the recipients are summarized in Table 1.

After fasting for a minimum of 2 h and resting for 15 min before assessment, unstimulated whole saliva was collected for 15 min in a graded test tube (Sarstedt, Nümbrecht, Germany). Stimulated whole SFR was determined by chewing a neutral paraffin wax (0.9 g) (Orion, Espoo, Finland) for 1 min while swallowing all the saliva, followed by a 5-min period of chewing a new piece of wax and collecting the produced saliva. The unstimulated/stimulated SFR was calculated in mL/min. Unstimulated SFR of $\leqslant$0.1 mL/min and stimulated SFR of $\leqslant$0.7 mL/min were defined hyposalivation.[6]

In order to determine tear production, the standard Schirmer's test without topical anesthesia was performed. Standardized strips of filter paper were placed in the lateral cantus away from the cornea and left in place for 5 min with the eyes closed. Readings were reported in mm of wetting for 5 min. The readings of $\leqslant$5 mm were considered as pathologic. Blood samples, including antinuclear Ab and rheumatoid factor profiles for Sjögren's disease were taken from recipients and donors.

During the clinical examinations, the subjects were asked about sicca symptoms (eye, mouth and skin). All participants filled in the social functioning (SF)-36 health survey[26] consisting of 36 questions, of which eight subscales and two summary scores were formed. Of the eight subscales, physical functioning, role physical and bodily pain contribute to the scoring of the physical component summary. Mental health, role emotional, and SF contribute to the scoring of the mental component summary. Three of the subscales, that is, vitality, general health and SF, have noteworthy correlations with both of the summary scores.[27,28] Norm-based scoring using a simple linear transformation of SF-36 scores for comparison with population norms was done. Data on QoL were already published elsewhere.[25] In the present study, the evaluation of data on QoL was restricted in report to sicca syndrome.

Donor and recipient characteristics were compared by Pearson's χ^2 test or by Fisher's exact test for categorical variables, and by Wilcoxon signed rank test for continuous variables. The Mann–Whitney *U* test was used for continuous variables when data were not paired. Score-based measures are reported as medians and interquartile ranges. All *P*-values reported are two-sided and were considered significant if $<$0.05. No adjustment for multiple testing was performed.

RESULTS

The mean unstimulated and stimulated whole SFRs of the recipients and donors are presented in Figure 1. Poor unstimulated SFR of $\leqslant$0.1 mL/min was found in 11% ($n=5$) of the long-term survivors of HSCT and in 2% ($n=1$) of their respective donors ($P=0.08$). Stimulated SFR$\leqslant$0.7 mL/min was observed in 20% ($n=9$) of the recipients and 7% ($n=3$) of the donors ($P=0.06$). In both donors and recipients, hyposalivation determined as unstimulated SFR $<$0.1 mL/min correlated to the subjective mouth dryness, whereas no correlation between stimulated SFR below 0.7 mL/min and subjective sicca symptoms was found (Table 2).

Forty-five percent of recipients compared with 27% of donors had a pathologic Schirmer's test ($<$5 mm) ($P=0.07$). Nevertheless,

Table 1. Overview (number of subjects and %) of the characteristics of the recipients and donors

Characteristics	*Recipients (n = 44)*	*Donors (n = 44)*
Sex		
Female	20 (45.5%)	24 (54.5%)
Male	24 (54.5%)	20 (45.5%)
Age (median)		
At the time of HSCT (range)	26.8 (5–50)	
At the time of examination (range)	44.3 (24–63)	43.4 (22–61)
Diagnosis		
Acute myeloblastic leukemia	16 (36%)	
CML	11 (25%)	
ALL	7 (16%)	
Non-Hodgin lymphoma	3 (7%)	
CLL	1 (2%)	
Myelodysplastic Syndrome	2 (45%)	
Severe aplastic anemia	4 (10%)	
TBI		
Yes/ no	39 (89%)/ 5 (11%)	
GVHD		
Acute: no or grade I/grade II–IV	18 (41%)/ 26 (59%)	
Chronic: yes/no	22 (50%)/ 22 (50%)	
On-going GVHD/ immunosuppression	9 (20%)/ 6 (14%)	
Karnofsky score		
100%	38 (86%)	43 (98%)
$<$90%	6 (14%)	1 (2%)

Abbreviation: HSCT = hematopoietic SCT.

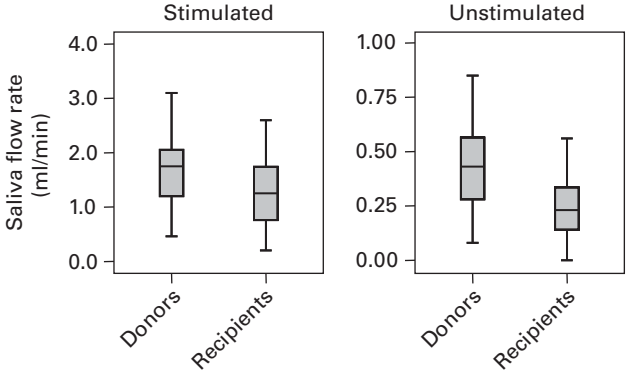

Figure 1. Mean stimulated and unstimulated whole SFR of the donors and recipients ($P<0.01$).

Table 2. Xerostomia and hyposalivation among HSCT recipients and donors (number of subjects (percentage))

Diagnosis	*Xerostomia*	*Hyposalivation*		*Both*
Criterion	Subjectively dry mouth	Non-stim. flow $\leqslant$0.1 mL/min	Stim flow $\leqslant$0.7 mL/min	Xerostomia and hyposalivation
Recipient	23 (52%)	5 (11%)[a]	9 (20%)	9 (20%)[b]
Donor	3 (7%)[c]	1 (2%)[a]	3 (7%)	2 (5%)

[a]All subjects demonstrating insufficient non-stimulated salivary flow rates showed stimulated flow rates below 0.7 mL/min. [b]Xerostomia and hyposalivation correlated with non-fractionated TBI ($P<0.001$) but not with the history of cGVHD. [c]With one exception in the donor group all subjects (recipients and donors) that suffered from hyposalivation complained subjective mouth dryness.

recipients showed no significant differences in tear production with a mean reading of 11 ± 1.6 mm compared with 13 ± 1.4 mm in the donors ($P=0.26$) for the drier eye.

Sicca symptoms were very common among HSCT recipients. Xerophthalmia was significantly ($P<0.001$) more common among the recipients (77%, $n=34$) than donors (16%, $n=7$). Dryness of the eyes was reported by 34 recipients and 6 donors ($P<0.001$) and xerostomia by 23 recipients and 3 donors ($P<0.001$). Dry skin was present in 32 patients and 11 donors ($P<0.001$). Sicca of eyes and mouth were significantly associated with each other ($P<0.001$). Eighty-four percent of the HSCT recipients ($n=37$) demonstrated two or more sicca symptoms in comparison with the 7% ($n=3$) of their respective donors ($P<0.001$). None of the study participants had positive antinuclear Abs nor the rheumatoid factor for Sjögren's syndrome. Also, none of the subjects (patients or donors) fulfilled diagnostic criteria for Sjögren's syndrome.[29]

Apart from severe cGVHD that was associated with dry mouth ($P=0.03$), history of GVHD or the presence of GVHD at presentation did not correlate with sicca symptoms nor with hyposalivation or a pathological Schirmer's test. Non-fractionated TBI correlated both with hyposalivation and xerostomia ($P<0.001$) (Table 2). These associations were independent from the the cGVHD status.

The mean SF-36 scores of the donors were significantly higher than those of the recipients for subscales physical functioning ($P<0.05$), bodily pain ($P<0.05$), general health perception ($P<0.001$), vitality ($P<0.05$) and physical component summary ($P<0.01$).[25] Amongst the recipients the following factors were significantly correlated with QoL subscales: unstimulated and stimulated SFR, dry skin and GVHD on physical functioning, xerostomia on physical role, xerostomia and dry skin on bodily pain, saliva flow and dry skin on general health, oral sicca on vitality, oral sicca and a pathological Schirmer's test on social functioning and xerostomia on emotional role. Consequently oral sicca and dry eyes and dry skin had an impact to the physical but not mental component summary (Table 3). No associations between sicca and QoL were observed among the donors.

DISCUSSION

The present study shows that, saliva and tear-flow rates as well as sicca symptoms (xerostomia, xerophthalmia and dry skin) are significantly affected in this unique cohort of very long-term survivors of HSCT, when compared with their respective sibling donors. We further demonstrate that the sicca symptoms and their objective findings correlate with QoL: Sicca symptoms were clearly associated with poorer QoL, with reduced physical but not mental functioning among the recipients.

In the current study, HSCT recipients had markedly lower unstimulated and stimulated salivary flow rates than the donors. Hyposalivation is a common acute and long-term complication of antineoplastic therapies of head and neck.[8,30] In HSCT-treated patients, radiotherapy is likely to be one etiological factor for hyposalivation.[9] Hypofunction of salivary glands depends on the cumulative dose to the gland tissue, and exposure to high total radiation doses ($>$26–36 Gy) leads to a significant reduction of salivary secretion.[31–33] However, as observed in our previous study, even lower radiation doses (6×2 Gy) used as conditioning therapy before HSCT may contribute to hyposalivation.[9] Comparable complications caused by TBI have been reported in other studies among adults and children.[34–36] In the current study, the observed hyposalivation may partly be due to permanent destruction and dysfunction of the glandular tissue caused by non-fractionated TBI, as 89% of the recipients had received such treatment. In this regard, non-fractionated TBI was identified as the major risk factor in the present study (Table 2). However, also fractionated TBI used as conditioning therapy can induce xerostomia.[37] Subjective reports of oral dryness obtained in a survey study among lymphoma patients after autologous HSCT (mean: 6 years after the therapy), reported xerostomia to be much more common in survivors who had received TBI as a part of their conditioning regimen in comparison with those without TBI.[38] In the current study, xerostomia was reported by 77% of the recipients but only by 9% of the donors. Thus, in our long-term survivors, xerostomia appears to be not only a common but also a persisting complication after HSCT.

Our results showed that HSCT recipients had a lower Schirmer's test score as well as subjective dry eyes more often than the donors. Ocular symptoms, cataracts, conjunctivitis and xerophthalmia have been shown to be common among HSCT recipients shortly as well as several years after the allogeneic transplantation.[7,39–41] Sixty percent of the long-term survivors had a pathological Schirmer score and 79% of the recipients suffered from xerophthalmia. Similarly to hyposalivation, GVHD also decreases the flow of lacrimal fluid. Recent studies on HSCT recipients with GVHD have reported the prevalence of pathological Schirmer's scores of $\sim$70% during the observation periods of 6 months to 3 years.[11,39] The present study indicates that this complication has an irreversible nature and that conditioning regimen may have a major role, as past or present GVHD did not correlate with sicca symptoms nor with a pathological Schirmer's test. The impact of the conditioning regimen (TBI) in the development of other ocular late effects, such as cataracts, has been well described.[41]

HSCT recipients frequently develop cutaneous manifestations and skin rashes due to GVHD, infections and drug reactions.[42] GVHD in particular is a major etiological factor in cutaneous manifestations, as skin is affected in almost all patients with GVHD.[43] In the current study, patient-assessed dry skin was very common, 72%, among the long-term survivors of HSCT. In addition, vast majority of the HSCT recipients (84%) demonstrated two or more subjective sicca symptoms (dry skin, dry eyes or dry mouth). As the skin is a very accessible organ, assessing dry skin by dermatologists may have an important role in diagnosing other sicca symptoms. Additionally, the dentist detecting xerostomia or hyposalivation may contribute in the diagnosis of other sicca symptoms.

This is the first study assessing sicca symptoms on long-term survivors and their impact on QoL using a validated instrument, that is, the SF-36.[25] Sicca symptoms were clearly associated with poorer QoL with particular impact on the physical component

Table 3. Factors that affect the subscales of the SF-36 of HSCT recipients

	Physical components of QoL				*Mental components of QoL*				*Physical component summary*	*Mental component summary*
	Physical functioning	*Role physical*	*Bodily pain*	*General health*	*Vitality*	*Social functioning*	*Role emotional*	*Mental health*		
Non-stim. SFR										
Good ($n=39$)	55 (53–57)	56 (56-56)	100 (72–100)	**77 (65–87)**	**65 (50–80)**	100 (75–100)	100 (100-100)	80 (72–92)	**56 (51–58)**	55 (49–58)
Poor ($n=5$)	45 (26–53)	37 (31–56)	64 (57–100)	**35 (33–54)**	**38 (63–94)**	63 (38–94)	76 (17–100)	64 (37–90)	**45 (37–49)**	43 (30–56)
P	0.05	0.09	0.47	**0.001**	**0.02**	0.05	0.10	0.22	**0.003**	0.15
Stim. SFR										
Good ($n=35$)	**55 (53–57)**	56 (56-56)	100 (72–100)	**77 (65–92)**	65 (50–80)	100 (88–100)	100 (100-100)	80 (68–92)	**57 (51–58)**	54 (49–58)
Poor ($n=9$)	**46 (30–52)**	56 (36–56)	100 (57–100)	**52 (36–77)**	50 (40–68)	75 (44–100)	100 (50–100)	80 (54–88)	**48 (39–51)**	53 (39–58)
P	**0.003**	0.42	0.73	**0.01**	0.07	0.05	0.17	0.59	**0.01**	0.55
Dry mouth										
No ($n=19$)	55 (53–57)	**56 (56-56)**	100 (74–100)	77 (62–87)	**70 (60–80)**	**100 (100-100)**	100 (100-100)	80 (68–88)	**57 (54–59)**	54 (49–58)
Yes ($n=23$)	53 (45–57)	**56 (38–56)**	84 (51–100)	72 (45–87)	**55 (40–65)**	**88 (63–100)**	100 (67–100)	84 (64–92)	**51 (44–58)**	53 (42–57)
P	0.09	**0.003**	0.06	0.15	**0.02**	**0.003**	0.05	0.93	**0.01**	0.47
Schirmer path										
No ($n=17$)	55 (53–57)	55 (46–57)	100 (74–100)	82 (62–95)	65 (55–80)	**100 (100-100)**	100 (100-100)	76 (70–84)	56 (52–59)	54 (49–60)
Yes ($n=25$)	55 (46–57)	56 (53–56)	100 (63–100)	77 (62–85)	60 (48–80)	**100 (63–100)**	100 (83–100)	84 (64–92)	55 (48–58)	55 (42–58)
P	0.26	0.14	0.76	0.34	0.50	**0.03**	0.14	0.56	0.38	0.95
Dry eyes										
No ($n=9$)	55 (53–57)	56 (56-56)	100 (68–100)	82 (67–92)	65 (53–80)	100 (100-100)	100 (100-100)	76 (66–86)	58 (52–61)	54 (48–58)
Yes ($n=34$)	55 (46–57)	56 (49–56)	92 (64–100)	75 (54–87)	60 (45–76)	100 (75–100)	100 (100-100)	82 (67–89)	55 (48–58)	54 (45–58)
P	0.26	0.23	0.44	0.26	0.53	0.13	0.71	0.55	0.06	0.85
Dry skin										
No ($n=11$)	**57 (55–57)**	56 (56-56)	**100 (100-100)**	**87 (72–92)**	65 (60–80)	100 (100-100)	100 (100-100)	92 (72–92)	**58 (56-59)**	56 (49–59)
Yes ($n=32$)	**53 (45–55)**	56 (51–56)	**79 (55–100)**	**72 (53–82)**	60 (45–79)	100 (75–100)	100 (75–100)	80 (64–100)	**53 (48–58)**	54 (44–57)
P	**0.005**	0.39	**0.04**	**0.02**	0.24	0.21	0.23	0.09	**0.01**	0.42
cGgHD ever										
No ($n=22$)	55 (53–57)	56 (49–56)	100 (72–100)	75 (62–83)	63 (45–80)	100 (75–100)	100 (92–100)	80 (68–92)	56 (51–58)	54 (49–57)
Yes ($n=22$)	53 (46–56)	56 (56-56)	92 (60–100)	77 (51–92)	50 (63–80)	100 (72–100)	100 (100-100)	82 (64–89)	54 (48–59)	56 (45–58)
P	0.08	0.33	0.43	0.81	0.93	0.92	0.51	0.95	0.51	0.51
cGVHD current										
No ($n=35$)	**55 (53–57)**	56 (56-56)	100 (72–100)	77 (62–92)	65 (45–80)	100 (75–100)	100 (100-100)	80 (68–88)	58 (50–58)	54 (49–57)
Yes ($n=9$)	**46 (41–55)**	56 (35–56)	100 (41–100)	72 (42–80)	60 (43–75)	88 (63–100)	100 (67–100)	76 (70–92)	51 (38–57)	53 (42–60)
P	**0.01**	0.17	0.75	0.11	0.55	0.41	0.80	0.80	0.16	0.55

Abbreviations: SFR = saliva flow rates; QoL = quality of life. No associations of any sicca symptoms with QoL were observed among the donors. Significant differences ($P<0.05$) are marked in bold.

summary among the recipients compared with their HLA-identical sibling donors. Reduced QoL measured with the SF-36 was found in a cohort of patients suffering from Sjögren's syndrome, a disease with comparable symptoms with cGVHD.[44]

In conclusion, within the limitations of the number of subjects studied, sicca symptoms and/or reduced saliva and lacrimal fluid flow were common long-term complications after HSCT. They were not necessarily a consequence of GVHD. They are also due to partially irreversible destruction of the glands during conditioning. The recipients had poorer QoL in comparison with the sibling donors and amongst the recipients sicca was associated with poorer QoL. As saliva and tears have several protective functions in the mouth, eyes and the skin, a reduced flow may cause infectious diseases, including generalized dental caries, periodontitis, conjunctivitis and yeast infections. Thus, the detection of sicca syndromes should result in preventive measurements of HSCT recipients. Furthermore, proper management of sicca symptoms is of paramount importance in optimizing the QoL and psychosocial adjustment of long-term survivors of HSCT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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