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Review

Salivary Changes before and after Hematopoietic Stem Cell Transplantation: A Systematic Review

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A B S T R A C T

Severe oral problems, including oral mucositis (OM) and xerostomia, often occur after conditioning therapy for hematopoietic stem cell transplantation (HSCT). Saliva plays a major role in protecting the oral mucosa and teeth. Alterations in salivary flow rate or salivary components resulting in decreased salivary defence mechanisms may affect oral/mucosal health and may influence the severity of OM. A systematic review was conducted to assess the current scientific knowledge on changes in salivary function and composition before and after HSCT. All English or Dutch articles examining salivary flow rate or salivary components before and after HSCT were included after title/abstract selection by 2 independent reviewers (weighted κ = .91). After quality assessment and exclusion of all research groups with both children age <14 years and adults, 33 articles were included for data analysis. Overall, the salivary flow rate was decreased at several days and months after HSCT. Although several salivary components were studied, most components were examined in only 1 or 2 studies with different patient populations or at different time points after HSCT. At 7 days after HSCT, albumin and proinflammatory cytokines were increased, whereas secretory IgA and components of the salivary antioxidant system were decreased. Secretory IgA levels were still reduced at 1 month after HSCT but returned to pre-HSCT values at 6 months after HSCT. Lactoferrin, secretory leukocyte protease inhibitor, and β_2-microglobulin levels were increased at 6 months after HSCT. Our findings show that changes in saliva reflect an inflammatory response occurring immediately after HSCT, followed by evidence of increased salivary antimicrobial defense mechanisms by 6 months after HSCT.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is used in the treatment of leukemia, lymphoma, and other severe blood diseases and may be either autologous or allogeneic, depending on the stem cell graft source. Before HSCT, patients receive conditioning therapy consisting of high-dose chemotherapy and/or radiotherapy.

A common oral complication in the early days after HSCT as a result of this conditioning therapy is oral mucositis (OM). OM is characterized by erythema, swollen mucosa, and ulcerations. In severe cases, it is extremely painful, which may affect the patient's ability to eat, drink, and/or sleep. In such cases, the use of opioids for pain relief is often required, and there is an increased risk of severe systemic infections due to ulcerations

[1]. Despite recent advances in the development of reduced-intensity conditioning therapy regimens, OM remains prevalent, with severe OM (score 2 to 4) seen in 50% to 70% of HSCT recipients [2,3].

Another common complication after allogeneic HSCT is chronic graft-versus-host disease (cGVHD), which occurs within several months after HSCT in approximately 25% to 80% of patients [4]. It can affect multiple organs, with commonly affected sites including the skin, mouth, and liver [5]. Oral cGVHD is characterized by lichenoid lesions, erythema, and ulcerations, and subjective complaints include pain, taste changes, and sensitivity. The salivary glands also may be affected, resulting in hyposalivation and xerostomia [6,7].

Saliva, a mixture of mainly water, ions, and proteins, protects the teeth and oral mucosa through buffering capacity, remineralization, and antimicrobial actions. Such proteins as defensins, cystatins, lactoferrin, and the immunoglobulins are important for this antimicrobial action [8]. Alterations in the function and/or composition of saliva resulting in decreased salivary defense mechanisms may affect oral/mucosal health

[9,10]. This systematic review was performed to evaluate the current scientific knowledge regarding changes in salivary function and protein composition before and after HSCT.

METHODS
Search Strategy

A literature search extending up to August 2017 was conducted by an investigator in consultation with a medical librarian in the electronic data-bases Embase, MEDLINE, and Web of Science. Search terms (including MeSH [Medical Subject Headings] terms, Emtree terms, and free text terms) related to hematopoietic stem cell transplantation and saliva were used for a search in title, abstract, and authors' keywords. The search terms were identified using index terms of previously identified key articles (Table 1).

Selection Criteria

All articles written in English or Dutch were selected from the electronic search based on title and abstract by 2 independent investigators. All articles assessing salivary function and/or components (eg, flow rate, proteins, cytokines) in patients undergoing HSCT or bone marrow transplantation were selected, and full text was obtained for quality assessment. For the selection on title and abstract, articles were scored with "no," "?," or "yes." In case of one "?" or disagreement, a consensus was reached. A third investigator could be consulted in the event of disagreement.

Quality Assessment and Data Extraction

Quality assessment was performed using a checklist based on the STROBE checklist with the explanatory article [11,12]. Eighteen items from this check-list (method, results and discussion section) were used for the quality assessment. If an item was not properly recorded, this was considered a potential source of bias. All items described properly were scored with a "+," corresponding to 1 point. All articles with ≥10 points were included for data extraction and data analysis.

Data Extraction and Analysis

Data extraction was performed by an investigator using an extraction form and included the number of patients, age range of the study population, type of conditioning therapy/stem cell transplantation, saliva collection method, salivary analysis method, time points of collection (day 0 is day of HSCT), and data on flow rate and salivary components. All studies with children in the study population were checked separately for age range of the participants. Studies with only children or studies with children age ≥14 years were included in the analysis. All other studies with children and adults that did not separately report the results in the 2 groups were excluded from data analysis due to the differences in salivary composition between children and adults (11 articles) [13].

The Psy package, version 1.1 was used with R version 3.4.1 (R Institute for Statistical Computing, Vienna, Austria) to calculate the squared weighted κ value for the agreement between the 2 investigators in the selection of articles.

RESULTS
Selection of Articles

The search yielded a total of 780 articles (with publication dates ranging from 1964 to 2017), of which 570 articles remained after removal of duplicates and language selection (Figure 1). Selection on title and abstract by 2 independent investigators resulted in 75 articles for full text and quality assessment (weighted κ = .91). Studies with low-quality or no follow-up after HSCT or control group were excluded. Finally, a total of 33 articles were included for data analysis.

The time points of assessment after HSCT varied among the articles. Some studies performed assessment in the early days after HSCT and other studies performed assessments several months after HSCT. No studies including an adult study population combined both short-term and long-term assessments.

Flow Rate

A total of 12 articles measured salivary flow rate in adult HSCT recipients in relation to time after HSCT, GVHD, OM, and/or conditioning therapy (Supplementary Table S1). Another 10 articles measured salivary flow rate in children or children age ≥14 years and adults (Supplementary Table S2). Overall, a trend toward decreased salivary flow rates was seen several days to months after HSCT compared with pre-HSCT levels in autologous and allogeneic HSCT recipients (Figure 2; Supplementary Tables S1 and S2) [14–17]. In the early days after HSCT, 1 study found an increase at days +8/+10 in allogeneic HSCT recipients [18], while no differences in salivary flow rates were seen in autologous and allogeneic HSCT recipients [19,20]. Overall, salivary flow rates appeared to improve over time; however, the studies are conflicting with respect to the time span. Improvement of salivary flow rate was reported at 2 and 12 months after autologous and allogeneic HSCT [17,21], whereas a decrease at around 3 months after allogeneic HSCT was found in another study [18] (Figure 2).

Along with the trend toward decreasing salivary flow rate, hyposalivation and xerostomia are frequently seen in autologous and allogeneic HSCT recipients. Compared with healthy controls, hyposalivation was more prevalent in adult autologous and allogeneic HSCT recipients before HSCT and at 6 and 12 months after HSCT [21]. Two other studies including children age ≥14 years and adults also found high prevalences of hyposalivation and xerostomia up to 12 months [22] and 1095 days [23] after HSCT. Several years after HSCT, hyposalivation and xerostomia were still prevalent in children [24].

Salivary dysfunction was seen in unstimulated and stimulated glandular saliva of adult HSCT recipients with aGVHD compared with age- and sex-matched individuals and HSCT recipients without GVHD [25]. Conflicting results for salivary flow rate were found in patients with oral cGVHD. A decreased unstimulated whole salivary (UWS) flow rate was found in patients with aGVHD [17] and those with oral cGVHD (with mucosal lesions, xerostomia, and restricted mouth opening as symptoms) [26,29], whereas no difference in UWS flow rate was reported in 2 studies in which only mucosal lesions were

Table 1
Search Terms used in the Literature Search

| MeSH terms	Emtree Terms	Text Terms
Cord blood stem cell transplantation Hematopoietic stem cell transplantation	(Allogeneic/autologous) hematopoietic stem cell transplantation	Hematopoietic stem cell transplantation
Peripheral blood stem cell transplantation	(Allogeneic/autologous/cord blood/peripheral blood/ nonmyeloablative) stem cell transplantation	HSCT
Bone marrow/transplantation	(Allogeneic/autologous) bone marrow transplantation	ASCT
Saliva	Saliva/saliva analysis/ hyposalivation	Saliva
Salivary proteins and peptides/histatins/mucin-5b/ salivary amylases/salivary cystatins/salivary proline-rich-proteins	Saliva protein/proline-rich protein/alpha amylase saliva isoenzyme	Salivary proteins/mucin/ histatin/salivary alpha amylase/cystatin/proline-rich proteins
Salivary glands/parotid gland/salivary ducts/salivary glands, minor/sublingual gland/submandibular gland/von Ebner glands	Salivary gland function/ salivation disorder/salivary gland/minor salivary gland/ parotid salivary gland/salivary gland duct/sublingual gland/ submandibular gland/von Ebner gland	Parotid gland/sublingual gland/submandibular gland
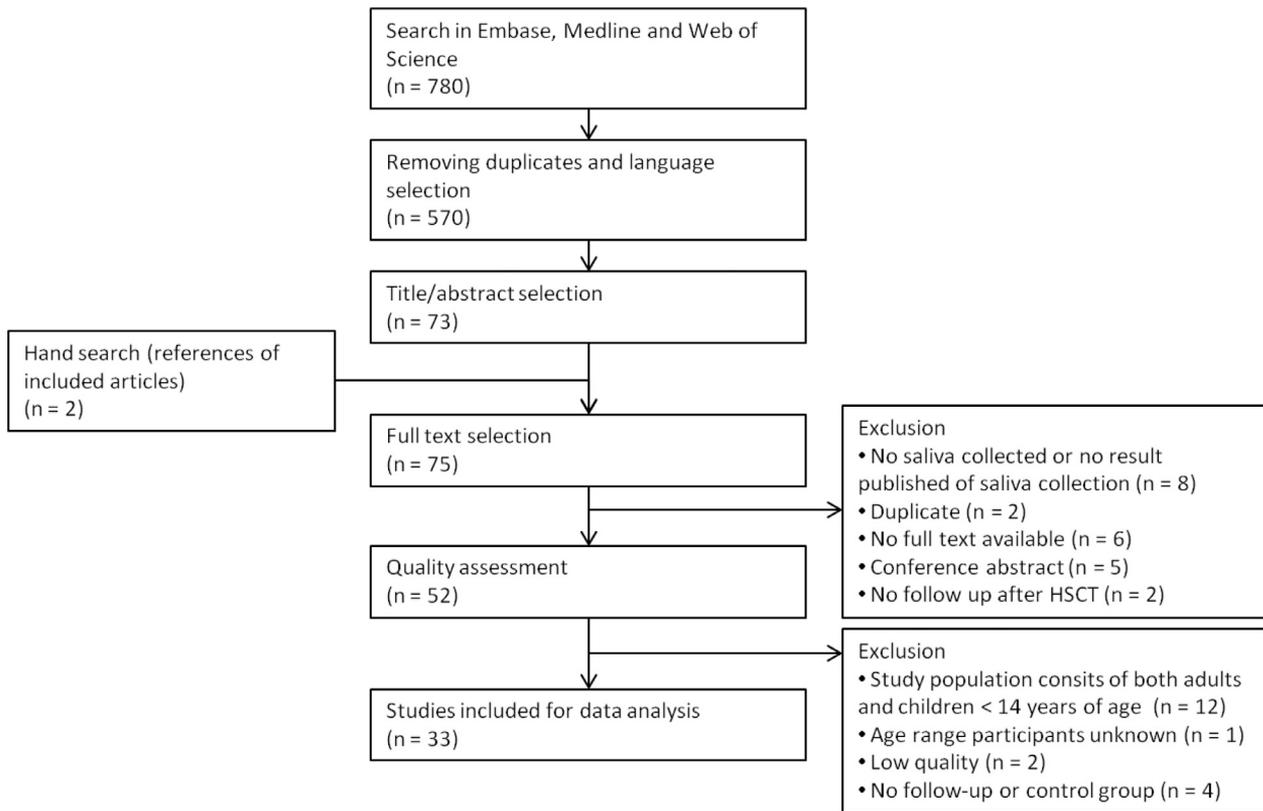
Figure 1. Flow diagram of the article selection process.

included as oral cGVHD symptoms [27,28] (Supplementary Table S1).

Only 2 of 4 included articles studying OM and salivary flow rate calculated a correlation or determined differences in patients with OM and those without OM. No correlation or differences in salivary flow rate were found between patients with OM and those without OM [14,15].

The studies including only children in the study population compared salivary flow rate in groups that received different conditioning regimens (Supplementary Table S2). The use of total body irradiation (TBI) in the conditioning regimen resulted in decreased salivary flow rates several years after HSCT compared with the use of only chemotherapy as conditioning therapy [30−32]. The administration of TBI over several days (ie, fractionated TBI) resulted in higher salivary flow rates at 1 year after HSCT [33] compared with single-session TBI; however, in 1 study in patients at the age of 15 and at 2 to 14.5 years after HSCT, no differences were found between the 2 TBI administration regimens [34]. A study including patients age ≥16 years found decreased salivary flow rates in UWS and
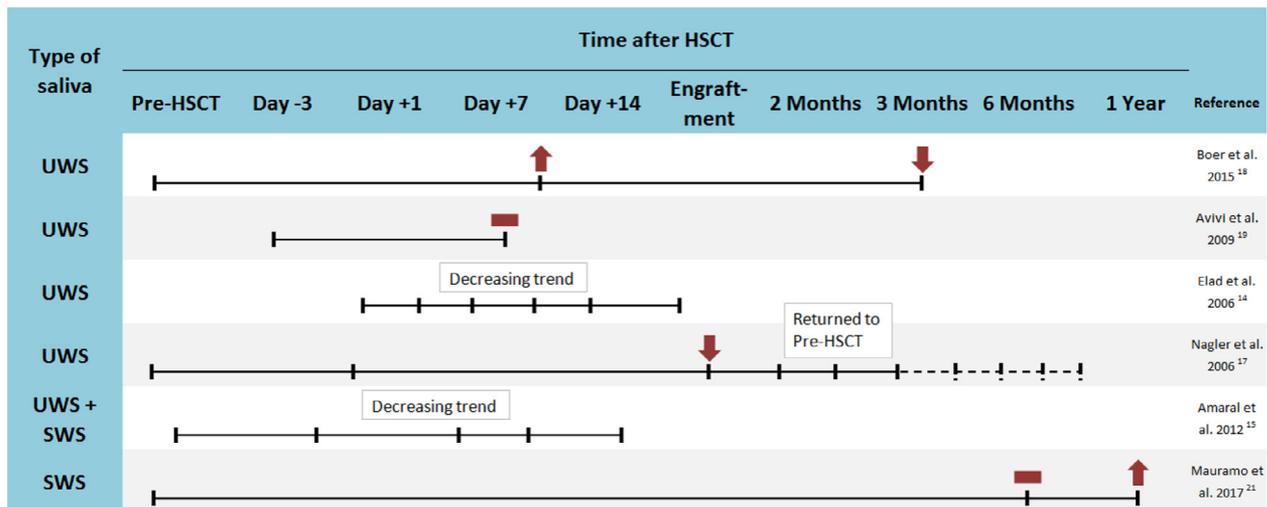

Figure 2. Changes in salivary flow rate after HSCT compared with before HSCT in adult HSCT recipients. ↑, increase; ↓, decrease; −, no change. The black horizontal line represents the time span of the study, and the small black vertical lines represent the time points of saliva collection. The black dashed line indicates that the study period was different for some patients in the study. Further details of the studies are provided in Supplementary Table S1.

stimulated whole saliva (SWS) in allogeneic and autologous HSCT recipients at 4 to 14 weeks after TBI in the longitudinal group, but no differences in salivary flow rates at 8 months to 7 years after TBI in the retrospective group [35].

Saliva Composition

Various salivary components have been studied after HSCT; however, most components were evaluated in only 1 or 2 studies with different study populations and/or time spans (Figure 3; Supplementary Table S3). The most studied type of saliva in the included studies was whole mouth saliva; only 2 studies evaluated glandular saliva (Supplementary Table S3).

Although there was no change in UWS total protein concentration in autologous HSCT recipients, several proteins were increased in UWS and stimulated submandibular (SM)/ sublingual (SL) saliva several days and months after autologous and allogeneic HSCT [10,17,19]. Increased albumin levels were found at day +7 in autologous HSCT recipients and at 1 month post-transplantation in allogeneic HSCT recipients [10,19]. In stimulated SM/SL saliva, increased levels of lactoferrin, secretory leukocyte protease inhibitor (SLPI), and β_2-microglobulin were seen 6 months after allogeneic HSCT [10] (Figure 3; Supplementary Table S3). At several days after autologous HSCT, several components of the salivary antioxidant system were decreased in UWS, leading to decreased salivary antioxidative capacities [17,19,36]. In addition, a decrease in secretory IgA was found at day +7 in UWS of adult autologous HSCT recipients and at 1 month after allogeneic HSCT in stimulated SM/SL saliva of adult patients [10,19] (Figure 3; Supplementary Table S3). In SWS, decreased levels of secretory IgA and IgG were found at 1, 2, and 3 months after autologous and allogeneic HSCT in children age ≥14 years and adults [37].

Overall, a trend toward increasing levels of proinflammatory cytokines, such as as TNF-α and IL-1, in the first days after autologous and allogeneic HSCT, although some contradictory results in salivary TNF-α levels in UWS and SWS have been reported [15,38,39] (Figure 3; Supplementary Table S3). Little is known about changes in the anti-inflammatory cytokines; only 1 study found increased levels of IL-10 in UWS and SWS of adult allogeneic HSCT recipients at days +7 and +14 [15]. Only limited research has been reported on other salivary components, such as matrix metalloproteinases, epidermal growth factors, and salivary prostaglandins (Supplementary Tables S3 and S4) [15,20,40].

In the study groups that included both children ≥ 14 years of age and adults, the salivary components were only studied once (Supplementary Table S4). Similar to the studies with only adults, an increasing trend was observed in UWS TNF-α, however a decreasing trend was observed for UWS IL-1β several days after autologous and allogeneic HSCT [20]. Increasing trends were also observed for the cytokines IL-6, CXCL8/IL-8 and IL-10 the metalloproteinase MMP2/TIMP-2 and the growth factors FGF, EGF and VEGF levels in UWS several days after autologous and allogeneic HSCT [20,41]. Decreasing trends were observed for myeloperoxidase (MPO) and the matrix metalloproteinase MMP9/TIMP-2 [20,41]. In aGVHD patients (children ≥ 14 years of age and adults) similar trends for total protein (no change) and uric acid (decreasing trend) were observed compared to the studies including only adult HSCT recipients [17].

In patients with cGVHD, increased levels of total protein, albumin, IgG, IL-1α, and IL-6 were found compared with healthy controls and age- and sex-matched allogeneic HSCT recipients without cGVHD [29,42,43] (Supplementary Table S3). Apart from targeted assays, a proteomics approach was also reported

for the discovery of biomarkers for cGVHD. Differently expressed proteins in UWS of adults with mucosal GVHD compared with patients without GVHD or healthy controls included IL-1 receptor antagonist, cystatin-B, lactoperoxidase, and lactotransferrin (Table 2) [27,28]. Mucin 16 and colony-stimulating factor 2 receptor β were also differentially expressed between adults with cGVHD (oral symptoms not specified) and healthy controls (Table 2) [44]. Moreover, 3 proteins S100A7, S100A8, and S100A9 short were differentially expressed between allogeneic patients with GVHD and those without GVHD and healthy individuals in a study including children age ≥14 years [45].

In addition to the compositional changes in proteins, changes in the inorganic components have been reported [18,19]; however, these changes were beyond the scope of this systematic review.

DISCUSSION

This systematic review was performed to assess the current scientific knowledge on changes in salivary function and composition before and after HSCT. Overall, salivary flow rate was decreased at several days and months after HSCT. In the first week after HSCT, levels of albumin and proinflammatory cytokines were increased, whereas levels of secretory IgA and components of the salivary antioxidant system were decreased. Increased levels of lactoferrin, SLPI, and β_2-microglobulin were found at 6 months after HSCT.

Although salivary flow rate appeared to show an overall trend toward reduction after HSCT, most studies assessing salivary flow rate in the first days after HSCT showed only a slight change in salivary flow rate. One explanation for this small change might be related to the type of conditioning therapy. In those studies, the conditioning therapy mostly involved chemotherapy; only some patients were treated with TBI in combination with chemotherapy in 2 studies [14,18]. As shown in a systematic review assessing salivary gland dysfunction and xerostomia in different cancer therapies, salivary gland dysfunction is less severe after chemotherapy than after radiation therapy [46]. A possible explanation for the significant increase in salivary flow rate found in the second week after HSCT in 1 study might be dysphagia caused by the conditioning therapy, as discussed by the authors [18].

A decreased salivary flow rate negatively affects the protective function of saliva and may result in oral complications. This probably explains the association observed between salivary hypofunction and oral mucositis [9]. Low salivary flow rates at baseline and during chemotherapy were identified as risk factors for OM in a study including 63 cancer patients receiving 5-fluorouracil as chemotherapy [47]. Furthermore, in the treatment groups of the intervention study included in this review, receiving a sialogogue therapy to stimulate salivary flow rate, less severe oral mucositis was found compared with that the control group [15]. In the first 2 weeks after HSCT, a trend toward decreasing salivary flow rate was also found in these treatment groups, but the decrease was less than that seen in the control group [15]. Moreover, higher values of salivary flow rate were found in the surviving patients in this intervention study [15].

Changes in the salivary composition after HSCT were also found. In the first 2 weeks after HSCT, a decreased salivary antioxidant capacity was reported [19,36]. The chemotherapeutic agents induce epithelial cell damage and consequently induce the generation of reactive oxygen species (ROS) [48]. One of the protective components in saliva is superoxide dismutase (SOD), which inhibits the production of free radicals [36]. In the first 2 weeks after HSCT, salivary SOD levels were
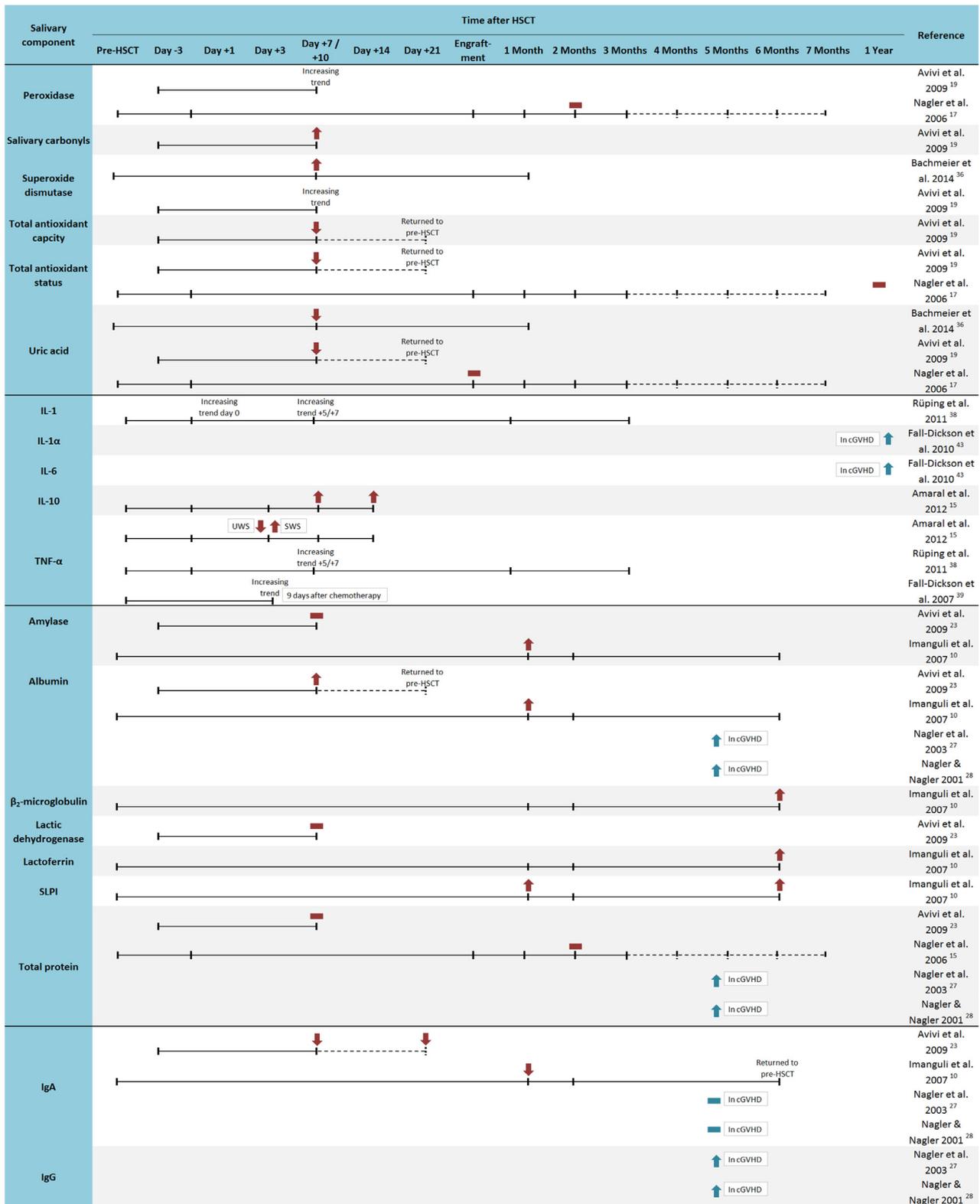
Figure 3. Compositional changes in saliva after HSCT compared with before HSCT in adult HSCT recipients. ↑, increase; ↓, decrease; −, no change. The black horizontal line represents the time span of the study, and the small black vertical lines represent the time points of saliva collection. The black dashed lines indicate that the study periods were different for some patients in that study. Changes in saliva represent changes in all types of saliva; saliva types are characterized in Supplementary Table S3.

Table 2
Potential Biomarkers Found on Proteomics Analysis of Saliva from Patients with GVHD

Reference	Patient Population	Type of Saliva	Proteomics Method	Total Proteins Found	Potential Biomarkers Found
Devic et al, 2014 [27]	20 patients with or without GVHD and 20 healthy adults (middle-aged and elderly)	UWS	Pooled samples, labeled with iTRAQ (4 groups), tandem TOF MS	249	Cystatin-B IL-1 receptor antagonist protein
Bassim et al, 2012 [28]	5 patients with moderate to severe oral cGVHD and 5 age-matched patients with cGVHD and no oral involvement (males only)	UWS	Pooled samples, targeted label-free quantification (LC-MS/MS)	180	Lactotransferrin, lactoperoxidase
de Souza et al, 2017 [44]	4 patients with GVHD and 4 healthy adult volunteers (women only)	UWS	SDS-PAGE and LCMS-ESI-IT-TOF mass spectrometry	Not reported	Mucin 16, colony-stimulating factor 2-receptor β

significantly increased in 1 study [19] and only marginally (not significantly) increased in another study [36], indicating compensation for the increased generation of ROS [19,36]. However, the compensation is not complete, as can be deduced from a decrease in total antioxidant capacity [19]. This decreased salivary antioxidant capacity might facilitate mucosal damage, as has been suggested in elderly patients, in whom it might be a risk factor for oral cancer [49].

Another factor that may promote oral mucosal damage is diminishing defense mechanisms, such as decreased levels of secretory IgA in the first 2 weeks after HSCT [19]. Oral mucosal damage is accompanied by increased levels of albumin, possibly due to increased permeability of the damaged mucosae reported within the first 2 weeks [19] and within 1 month after HSCT [10]. In mice lacking the secretory component of IgA, increased levels of the serum-born components albumin and IgG were found in whole saliva, also indicating increased mucosal permeability [50]. Although the knockout mice in that study lacked secretory IgA, their IgA levels, derived from serum and consisting only of the monomeric form instead of the dimeric secretory form of IgA normally found in saliva, were similar to those measured in wild-type mice [50].

Oral mucosal damage is not only seen in the first 2 weeks after HSCT, but also may occur several months after HSCT in allogeneic HSCT recipients with oral cGVHD. In patients with cGVHD, indications of increased membrane permeability were demonstrated by increased levels of albumin, total protein, and IgG [29]. A possible explanation for the oral mucosal damage in those patients might be decreased salivary antioxidant capacity, as described by Nagler et al [17].

In cGVHD, 3 different oral manifestations have been hypothesized to occur: mucosal cGVHD, restricted mouth opening, and salivary gland involvement [51]. In cases of salivary gland dysfunction, lymphocytic infiltrates are found in the salivary glands, leading to hyposalivation and compositional changes. The hypothesis of the 3 different oral manifestations of oral cGVHD may explain the conflicting salivary flow rate data in cGVHD patients in this review [18,25−29]. The compositional changes may be similar to those found in the saliva of patients with Sjögren's syndrome [10]. The increased levels of lactoferrin, β_2-microglobulin, and SLPI found in stimulated SM/SL saliva at 6 months after allogeneic HSCT may reflect salivary infiltrates [10].

Compositional changes in the saliva occurring in different forms of oral cGVHD are unknown. For the differences in total protein, albumin, IgA, and IgG reported in patients with cGVHD, the type of cGVHD was not specified. However, 2 studies that included patients with cGVHD with oral mucosal changes identified cystatin-B, IL-1 receptor antagonist protein, lactotransferrin, and lactoperoxidase as differently expressed

proteins in patients with mucosal cGVHD compared with cGVHD without oral involvement and healthy adults. For a better understanding of the compositional changes in saliva in cGVHD patients, separation of the different types of cGVHD is important, especially when studying compositional changes in saliva in cGVHD patients with salivary gland involvement. Moreover, prospective observational studies that include both short-term and long-term measurements in HSCT recipients are required.

In conclusion, overall the evaluated studies showed a trend toward decreasing salivary flow rate at both several days and several months after HSCT and reported compositional changes in saliva reflecting an inflammatory response directly after HSCT, followed by increases in salivary antimicrobial defense mechanisms at 6 months after HSCT. However, these conclusions are based on studies in differing study populations and different types of saliva collected at different follow-up times after HSCT. No single study included both short-term and long-term follow-up.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.01.026.

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