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Original Article

Prevalence and Characteristics of Taste and Smell Dysfunction in Patients with Chronic Oral Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation

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ABSTRACT

Chronic oral graft-versus-host disease (cGvHD) is a frequent late effect of allogeneic hematopoietic stem cell transplantation (alloHSCT). It can manifest through diverse oral complications such as mucosal abnormalities, impaired salivary gland activity, and restricted jaw movement. Sensory issues involving taste and smell may also arise; however, the occurrence, characteristics, severity, and their influence on quality of life (QoL) remain insufficiently defined. This study aimed to determine how common and severe taste and smell disturbances are, describe their characteristics, evaluate their effect on QoL, and explore whether altered sensory function is associated with oral mucosal cGvHD or hyposalivation. Individuals who had undergone alloHSCT at least 100 days earlier and were referred for symptoms linked to oral cGvHD were invited to participate in this cross-sectional investigation. Oral mucosal cGvHD signs were clinically scored, both stimulated and unstimulated saliva flow rates were recorded, and objective taste and smell assessments were performed. Self-reported sensory changes and measures of overall and oral-health–related QoL were also collected. Forty-five participants were enrolled. Objective testing showed reduced taste function (hypogeusia) in 68.9%, decreased olfactory function in 28.9%, and complete anosmia in 11.1%. Despite this, only 31.1% reported severe and 22% reported moderate taste disturbances, indicating that many were unaware of their deficits. Sensory impairments did not correlate with oral mucosal cGvHD or low salivary flow. Most recipients experienced diminished oral-health–related QoL; however, no clear association between sensory ability and either global or oral-health–specific QoL emerged. Taste and smell dysfunctions are frequent after alloHSCT. Although many patients report poorer oral-health–related QoL, the precise contribution of these sensory disturbances requires further clarification.

Keywords: Hyposalivation, Hypogeusia, Quality of life, Allogeneic hematopoietic stem cell transplantation, Chronic oral graft-versus-host disease, Chemosensory disturbances

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Introduction

Chronic graft-versus-host disease (cGvHD) is a well-recognized complication following allogeneic hematopoietic stem cell transplantation (alloHSCT) [1, 2]. Donor stem cells—obtained from peripheral blood, bone marrow, or umbilical cord blood—produce immune cells capable of eliminating malignant hematologic cells but may also attack healthy host tissues. This donor-driven immune response can involve multiple organs, commonly the skin, eyes, oral cavity, gastrointestinal tract, liver, lungs, musculoskeletal system, and genitourinary structures, often causing pain, functional limitations, and reduced quality of life (QoL) [1, 2].

The oral cavity is affected in 45–83% of individuals with cGvHD [1]. Symptoms may appear anywhere within the mouth or orofacial region and may include lichenoid mucosal changes, ulcerations, erythema, sensitivity or pain, mucoceles, salivary gland impairment, reduced mouth opening, and changes in taste perception (hypogeusia or dysgeusia) [1-6].

Flavor perception relies on an interplay between taste, smell, somatosensory input (e.g., temperature, texture), and psychological factors [7]. Taste buds identify five primary taste qualities: sweet and umami contribute to energy intake and eating pleasure; bitter helps detect harmful substances; and salty and sour aid in electrolyte and acid-base regulation [8]. Prior investigations report that 47% of alloHSCT recipients experience long-term, selective impairments in umami, salty, and sweet taste [4, 9].

Olfactory receptors of cranial nerve I, located deep in the nasal cavity, detect odor molecules that arise during chewing and swallowing. Both heightened odor sensitivity and total smell loss can interfere with appetite and enjoyment of food and drink [10].

Beyond smell loss, multiple factors may lead to taste alterations after alloHSCT, including conditioning-related toxicity, inflammation-related damage to taste buds from oral cGvHD, cranial nerve (VII, IX, X) neurotoxicity, shifts in oral microbiota, infectious or dental conditions, inadequate oral hygiene, medication side effects, reduced salivary secretion, and anxiety [11, 12].

Although some data suggest that taste and smell deficits occur in alloHSCT survivors, their frequency, severity, and relationship with oral cGvHD remain poorly characterized. These sensory deficits may contribute to inadequate nutrition and emotional distress, adversely influencing global and oral-health–related QoL (OH-QoL) [13, 14]. Consequently, this study investigates how common and severe taste and smell disturbances are among patients attending an oral GvHD clinic and examines their association with oral mucosal cGvHD, hyposalivation, and both global and oral-health–related QoL.

Materials and Methods

This cross-sectional study was carried out in the Department of Oral and Maxillofacial Surgery at Amsterdam University Medical Center, AMC location, from February 2019 through December 2020. Approval was granted by the Institutional Medical Ethics Committee (NL69437.018.19). All participants provided written informed consent. Patient information was anonymized before analysis and stored securely using Castor EDC (Amsterdam, The Netherlands).

Eligibility criteria

Patients who had undergone an alloHSCT for hematologic cancers at least 100 days earlier and were referred for concerns related to oral cGvHD were considered eligible. Participants needed to have either current or past oral symptoms associated with cGvHD. Individuals were excluded if they were active smokers, had pre-existing autoimmune diseases (e.g., Sjögren's syndrome or lichenoid granulomatous conditions), had neurodegenerative diseases (e.g., Parkinson's or Alzheimer's), or uncontrolled diabetes.

Oral examination

A clinical oral assessment was carried out to confirm the presence of oral cGvHD. These evaluations were performed by a dentist with expertise in oral complications of cancer patients (JR-D). Mucosal changes were scored using the NIH Oral cGvHD Activity Assessment Tool, which evaluates erythema, hyperkeratosis, ulcers, and mucoceles with a total score ranging from 0 to 15 [15]. A score of 0–2 indicated no cGvHD, whereas 3–15 pointed to the presence of oral cGvHD [16].

Questionnaires

A series of questionnaires were used to assess gustatory function, oral cGvHD symptoms (NIH), and QoL (EORTC QLQ–C30), along with oral health-specific QoL (EORTC QLQ–OH15 and OHIP-14).

The EORTC QLQ–C30's taste and smell addendum assesses self-reported changes in basic tastes (sweet, salt, sour, and bitter) sensitivity [17]. The answers were scored on a 4-point Likert scale: 1 (none), 2 (slightly), 3 (moderately), and 4 (strongly).

The NIH questionnaire tracks the severity of oral cGvHD symptoms (dryness, pain, sensitivity) at their worst during the last 7 days [15, 18], using an 11-point scale ranging from 0 (none) to 10 (worst imaginable).

The EORTC QLQ–C30 is a validated measure for cancer patients' global QoL, containing subscales for functional, symptom, and specific symptom-related items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial impact), all rated on a 4-point scale: 1 (none), 2 (slightly), 3 (moderately), and 4 (extensively). The global health status scale is assessed using a 7-point scale, from 1 ("very poor") to 7 ("excellent") [19, 20].

The EORTC QLQ–OH15, an extension of the QLQ–C30, specifically evaluates oral health-related QoL for cancer patients [21]. It includes 6 subscales: oral health QoL (8 items), information (2 items), dentures (2 items), and three individual items (sticky saliva, soreness, food sensitivity). Items are rated using a 4-point Likert scale: 1 (none), 2 (slightly), 3 (moderately), and 4 (strongly). The total score ranges from 11 to 44, with higher scores indicating poorer oral health-related QoL.

The OHIP-14 measures the social impact of oral health on overall QoL over the previous 30 days [22]. It consists of 7 dimensions: functional limitation,

physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicaps. Each item is scored on a 5-point Likert scale: 1 (never), 2 (rarely), 3 (sometimes), 4 (often), and 5 (always). The total score ranges from 14 to 70, with higher scores indicating worse oral health-related QoL.

Sialometry

Stimulated and unstimulated salivary flow rates and pH were measured. Prior to testing, participants were asked to avoid eating, drinking (except water), or practicing oral hygiene for at least 30 minutes. Testing occurred between 9:30 and 11:30 AM. Participants expectorated saliva continuously for 5 minutes into a pre-weighed tube. For stimulated saliva, participants chewed tasteless paraffin gum to enhance salivation, avoiding talking or swallowing during collection [23]. Salivary flow was recorded in grams per minute (g/min). Severe hyposalivation was identified when unstimulated flow was below 0.1 g/min or stimulated flow was below 0.5 g/min [24].

Taste evaluation

The Burghart taste strips (Medisense, Burghart Messtechnik, Wedel, Germany) were used to assess the oral cavity's taste sensitivity. The 16 taste strips were infused with four flavors (sweet, salty, sour, bitter) at varying concentrations. Each patient was given the strips in a specific sequence, and after placing the strip on the tongue and closing their mouth, they had to select the appropriate taste (sweet, sour, bitter, salt). If no flavor was detected, they reported it as flavorless. Hypogeusia was diagnosed if the total score was below 9 out of 16 [25].

Olfactory assessment

To evaluate the olfactory performance of patients, the Sniffin' Sticks test (Burghart Messtechnik, Wedel, Germany), a validated screening tool, was used [26]. This test helps differentiate between complete loss of smell (anosmia), reduced ability to smell (hyposmia), and normal smell function (normosmia). The test involved odor pens containing 12 different scents, such as lemon, coffee, and leather. Patients were instructed to hold the pen about 2 cm under their nose for 3–4 seconds. Afterward, they were presented with a card containing four possible answers and asked to select the one that best described the odor they smelled. Anosmia was diagnosed if the score was below 6 out of 12, and hyposmia was identified if the score ranged from 6 to 9 out of 12.

Statistical analysis

The associations between oral cGvHD, taste and smell impairments, salivary function, and quality of life were tested using the Fisher–Freeman–Halton exact test, Mann–Whitney U-test, and Kruskal–Wallis test. All data analysis was performed with IBM SPSS Statistics version 27 (IBM, Armonk, NY). A significance level of $p < 0.05$ was used.

Results and Discussion

Patient demographics

This study involved 45 alloHSCT recipients, with 44.4% women and 55.6% men **(Table 1)**. The average age of participants was 53 years (±14.7), and the most prevalent diagnosis was acute myeloid leukemia (30.8%). The patients had undergone their alloHSCT at least 100 days before the assessment. While one patient was transplanted over 10 years ago, most had received the procedure between 1 and 3 years prior. Treatment regimens and medications were adjusted to meet individual patient needs. On average, participants were taking 11.5 medications (±5.5), including antiviral, antifungal, antibacterial, and immunosuppressive drugs. Every patient was on at least one medication that could potentially influence their taste [27, 28].

Table 1. Patient and Treatment Characteristics

Characteristic	Value
Age (years)	53.27 ± 14.727 (Mean ± SD)
Gender	
Female	20 (44.4%)
Male	25 (55.6%)
Primary Diagnosis	
Acute myeloid leukemia	14 (30.8%)
Myelodysplastic syndrome	7 (15.4%)
Angioimmunoblastic T-cell lymphoma	3 (6.6%)
Mantle cell lymphoma	3 (6.6%)
Acute lymphocytic leukemia	2 (4.4%)
Chronic lymphocytic leukemia	2 (4.4%)
Sickle cell anemia	2 (4.css4%)
Multiple myeloma	2 (4.4%)
Non-Hodgkin lymphoma	2 (4.4%)
Other diagnoses	8 (17.6%)
Conditioning Regimen	
Myeloablative	11 (24.4%)
Non-myeloablative	14 (31.1%)
Reduced-intensity	20 (44.4%)
Time Since Transplantation (years)	
<1 year	12 (26.7%)
1–3 years	19 (42.2%)
3–5 years	8 (17.8%)
>5 years	6 (13.3%)
Stem Cell Source	

Peripheral blood progenitor cells	34 (75.6%)
Bone marrow	11 (24.4%)
Number of medications potentially affecting taste	11.5 ± 5.5 (Mean ± SD)

Oral cGvHD

At the time of assessment, all patients had either active oral cGvHD symptoms or a history of such symptoms treated in our clinic. The oral examination revealed that 24 patients (53.3%) had signs of oral mucosal cGvHD. The most frequently observed manifestations were lichenoid changes (40%) and erythema (36%), which were the most severe according to the NIH Activity Assessment tool. Ulcerations (11%) and mucoceles (13%) were less common and generally of mild to moderate severity **(Table 2)**. No patient had mucosal infections during the evaluation.

Table 2. Presence and Severity of Oral Mucosal cGvHD Scored by the Oral cGvHD Activity Assessment Tool [15]

	Severe	Moderate	Mild	Not present
Erythema	5 (11.1%)	1 (2.2%)	10 (22.2%)	29 (64.4%)
Lichenoid	5 (11.1%)	6 (13.3%)	7 (15.6%)	27 (60.0%)
Ulcers	1 (2.2%)	4 (8.9%)		40 (88.9%)
Mucoceles	0	3 (6.7%)	3 (6.7%)	39 (86.7%)

Regarding self-reported severity of oral cGvHD symptoms over the past 7 days, the highest average scores were for oral dryness (5.4 ± 2.9), followed by oral sensitivity during eating and drinking (4.0 ± 3.1), and oral pain (2.5 ± 3.0). Patients with objectively confirmed oral mucosal cGvHD reported significantly more oral pain (3.7 ± 3.1) compared to those without such manifestations (1.2 ± 2.1) (Mann–Whitney U-test, $p = 0.004$). Similarly, patients with oral mucosal cGvHD reported more oral sensitivity (4.9 ± 2.9) than those without (2.9 ± 3.1) (Mann–Whitney U-test, $p = 0.012$). There was no significant difference in reported dryness between the two groups (Mann–Whitney U-test, $p > 0.05$).

Taste

A majority of participants (68.9%) had reduced taste function (hypogeusia). While most could detect all four basic tastes (sweet, salty, bitter, and sour) at the highest concentrations, their ability to identify tastes diminished with decreasing concentrations on the test strips **(Figure 1)**. None of the patients had a complete loss of taste (ageusia).

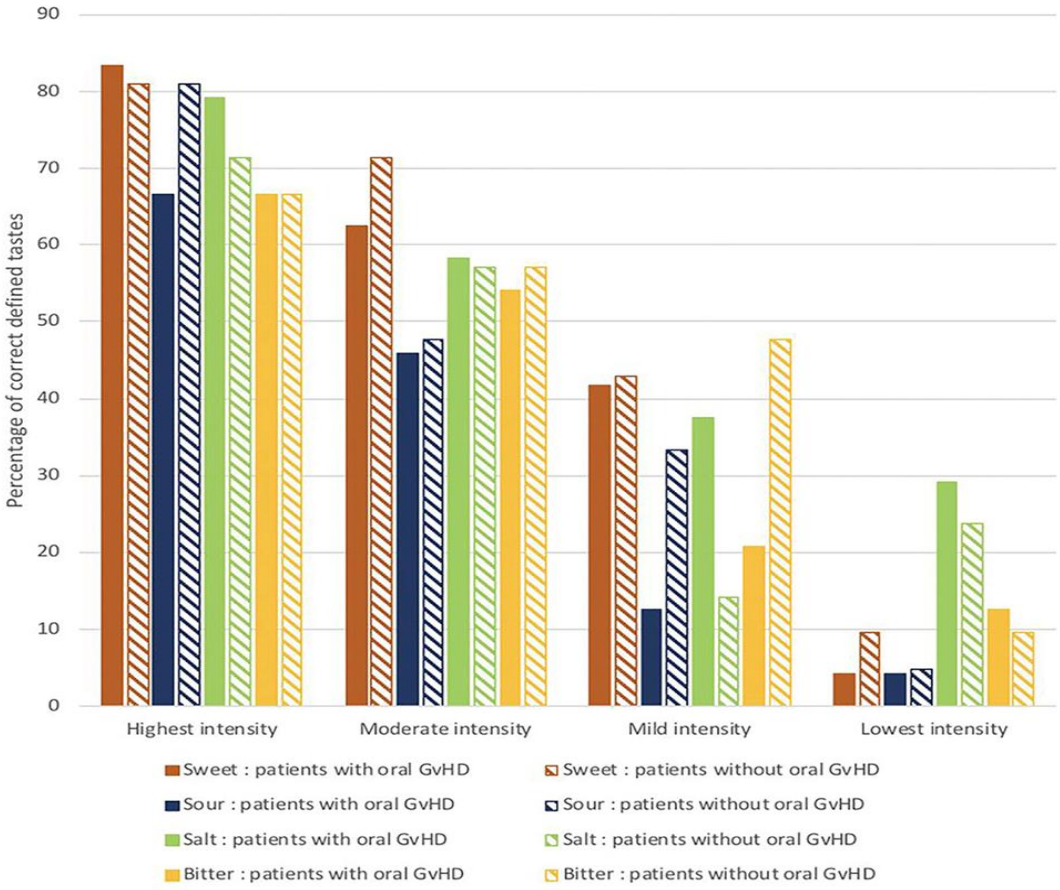

Figure 1. Percentage of correctly identified tastes at varying concentrations in patients with and without oral mucosal cGvHD (N = 45).

Among the patients, 31.1% reported severe taste changes, and 22% experienced moderate changes, often in the form of reduced taste sensitivity. An increased sensitivity to taste was noted by 13.3% of participants. Bitter and sour tastes were notably more pronounced in 24–29% of patients **(Figure 2)**.

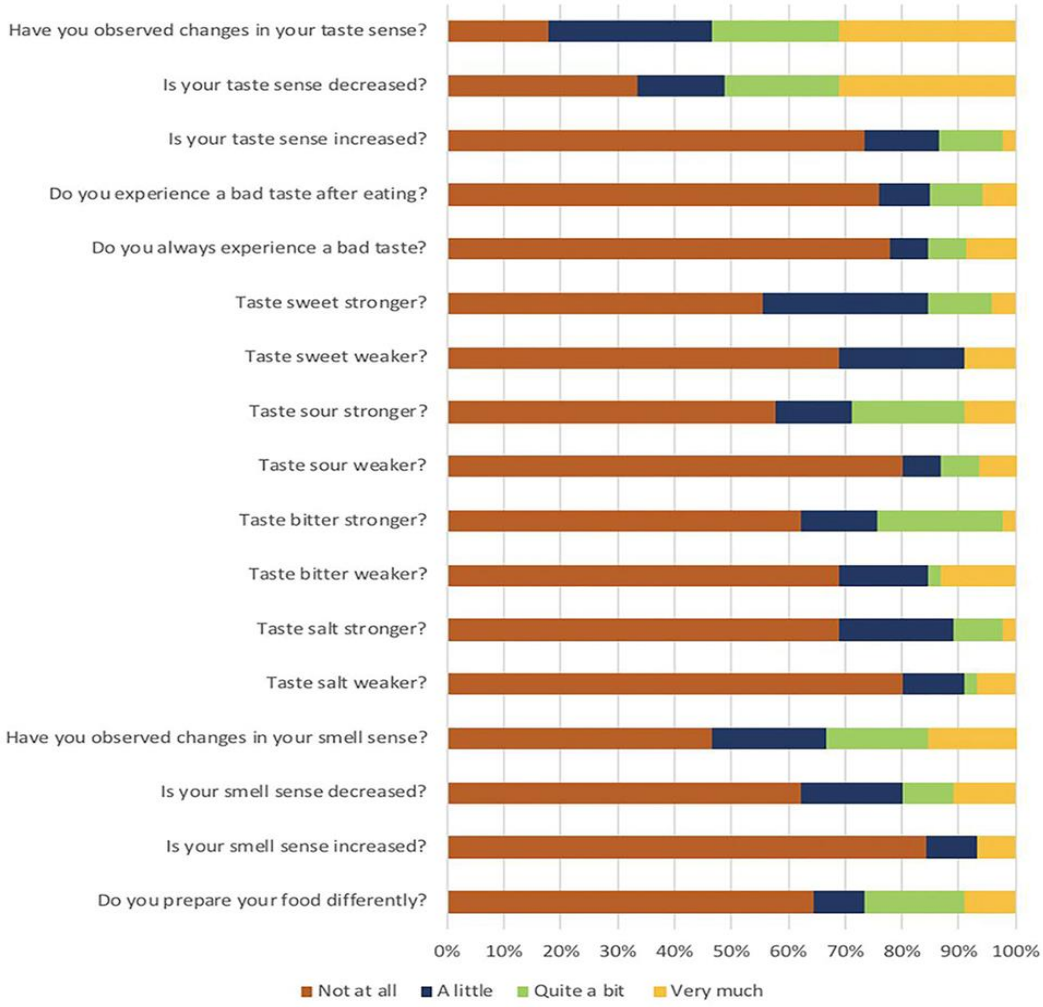

Figure 2. Distribution of responses to the taste and smell questionnaire from the EORTC QLQ–C30 (N = 45).

Taste sensitivity awareness

The discrepancy between objective measures and patient-reported taste perceptions suggests that individuals with hypogeusia were often unaware of their reduced taste. Not all patients with diminished taste recognition noticed the change. Comparing patients with and without oral mucosal cGvHD, no significant differences were observed in their ability to detect taste (**Table 3**, Fisher–Freeman–Halton exact test, $p > 0.05$).

Table 3. Distribution of oral mucosal cGvHD and hypogeusia (objective reduction in taste).

		Hypogeusia	Normogeusia	Total	Fisher's exact test (2-sides)	*P*-value
GvHD	**Present**	19	5	24		
	Not present	12	9	21	0.196	0.111
	Total	31	14	45		

Smell perception

Smell disturbances were detected in 40% of the patients (18 individuals), with 28.9% experiencing hyposmia (diminished ability to smell) and 11.1% experiencing anosmia (complete loss of smell). The odor that patients most frequently identified correctly was orange, followed by peppermint, while lemon was the least recognized **(Figure 3)**.

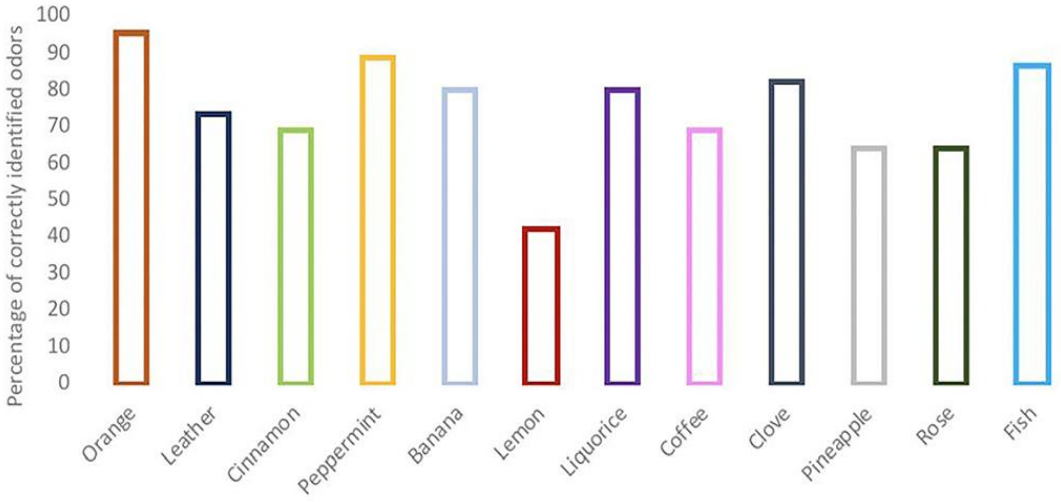

Figure 3. Outcomes of the clinical smell evaluation test.

About 15.6% of patients reported substantial changes in their sense of smell, 17.8% described moderate changes, and 20% mentioned minor changes. A small percentage (11.1%) reported a severe decline in smell sensitivity, while 6.7% felt an increase in their smell sensitivity **(Figure 2)**. Most patients with confirmed anosmia or hyposmia also experienced a decrease in smell sensitivity (Fisher–Freeman–Halton exact test, p = 0.002) or changes in smell perception more frequently than those with normal smell function (Fisher–Freeman–Halton exact test, p = 0.026). No significant difference in smell ability was found between patients with and without oral mucosal cGvHD (**Table 4**, Fisher–Freeman–Halton exact test, p > 0.05).

Table 4. Link between oral mucosal cGvHD and smell perception.

		Normosmia	Hyposmia	Anosmia	Total	Fisher-Freeman-Halton exact test	*P*-value
GvHD	**Present**	11	8	2	21		
	Not present	16	5	3	24	1.668	0.463
	Total	27	13	5	45		

Salivation and dry mouth

Approximately 85% of participants showed normal levels of both stimulated and unstimulated salivary flow. The average pH of unstimulated saliva was slightly lower than normal **(Table 5)**. A majority (75.6%) of patients reported experiencing xerostomia, or dry mouth, with 15.6% describing it as mild, 33.3% as moderate, and 26.7% as severe. No significant association was observed between salivary flow rates and the occurrence of taste or smell disturbances (**Table 6**, Fisher–Freeman–Halton exact test, p > 0.05).

Table 5. Classification of salivary flow.

Salivary Flow and pH Parameter	Stimulated Saliva	Unstimulated Saliva
Salivary flow rate		
Hyposalivation	7 (15.6%) < 0.5 ml/min	6 (13.3%) < 0.1 ml/min
Normal flow	38 (84.4%) ≥ 0.5 ml/min	39 (86.7%) ≥ 0.1 ml/min
pH value	6.9 ± 0.5 (Ref. 7.0–8.0)	6.2 ± 0.3 (Ref. 6.8–7.5)

Table 6. Correlation between taste and smell disturbances and salivary flow.

Taste / Smell Status	Normal Salivary Flow	Hyposalivation	Total	Statistic (Fisher-Freeman-Halton exact test)	P-value
Unstimulated saliva					
Hypogeusia	25	6	31	–	0.156
Normogeusia	14	0	14		

Total	39	6	45		
Anosmia	4	1	5	0.908	0.832
Hyposmia	12	1	13		
Normosmia	23	4	27		
Total	39	6	45		
Stimulated saliva					
Hypogeusia	26	5	31	–	1.000
Normogeusia	12	2	14		
Total	38	7	45		
Anosmia	3	2	5	2.701	0.307
Hyposmia	12	1	13		
Normosmia	23	4	27		
Total	38	7	45		

Quality of life

On average, patients rated their overall quality of life moderately high (67.2 ± 24.6 on the EORTC QLQ–C30) more than 100 days after transplantation. However, their oral health-related quality of life was reported lower (24.0 ± 16.0 on the EORTC OH-15). Most frequent issues included mouth soreness, ulcers at the mouth corners, dry mouth, food and drink sensitivity, taste issues, and trouble eating solid foods **(Table 7)**. There were no substantial differences in oral health-related quality of life between those with or without taste or smell disorders, or oral mucosal cGvHD symptoms ($p > 0.05$).

Table 7. Comparison of (oral health-related) quality of life and taste/smell issues.

Subscales	**cGvHD**				**Taste**			**Smell**		
	Not present	**Present**			**Hypogeusia**	**Normogeusia**		**Anosmia**	**Hyposmia**	**Normosmia**
	Mean ± SD	**Mean ± SD**	**Coefficient[a] / p-value**	**p-value**	**Mean ± SD**	**Mean ± SD**	**Coefficient[a] / p-value**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
EORTC QLQ-C30										
Global health status / QoL[c]	71.8 ± 20.7	63.2 ± 27.5	210.0 / 0.342	0.342	67.2 ± 24.6	69.6 ± 26.0	163.0 / 0.186	63.3 ± 32.6	70.5 ± 16.5	66.4 ± 27.0
EORTC QLQ-OH15										
Overall oral health-QoL[c]	19.6 ± 14.6	27.8 ± 16.6	182.0 / 0.112	0.112	24.0 ± 16.0	25.7 ± 16.7	180.5 / 0.377	25.8 ± 18.0	21.5 ± 10.7	24.8 ± 18.1
Sticky saliva[d]	22.2 ± 33.9	22.2 ± 33.6	251.5 / 0.997	0.997	22.2 ± 33.3	23.7 ± 36.7	215.0 / 0.948	20.0 ± 44.7	18.0 ± 25.9	24.7 ± 35.3
Sensitivity to food/drink[d]	41.3 ± 37.9	40.3 ± 29.5	249.0 / 0.943	0.943	40.7 ± 33.2	45.2 ± 35.0	168.5 / 0.235	46.7 ± 44.7	38.5 ± 32.9	40.7 ± 32.5
Sore mouth[d]	47.6 ± 42.9	48.6 ± 34.0	242.5 / 0.822	0.822	48.1 ± 37.9	49.5 ± 40.3	207.0 / 0.806	46.7 ± 50.6	43.6 ± 37.0	50.6 ± 37.4
OHIP-14										
Functional limitation[d]	3.7 ± 2.5	4.6 ± 2.0	179.0 / 0.086	0.086	4.2 ± 2.3	4.4 ± 2.3	178.0 / 0.329	5.6 ± 3.6	3.5 ± 2.0	4.3 ± 2.0
Physical pain[d]	4.2 ± 2.0	5.7 ± 2.7	173.0 / 0.069	0.069	5.0 ± 2.5	5.1 ± 2.4	200.0 / 0.681	6.0 ± 2.7	5.5 ± 2.8	4.6 ± 2.3
Psychological discomfort[d]	2.7 ± 1.2	3.5 ± 2.2	207.0 / 0.249	0.249	3.1 ± 1.8	3.4 ± 2.1	181.5 / 0.326	3.2 ± 1.8	3.2 ± 1.8	3.1 ± 1.9

Physical disability[d]	4.1 ± 2.6	4.5 ± 2.3	215.0 / 0.390	0.390	4.3 ± 2.4	4.4 ± 2.6	209.0 / 0.848	5.2 ± 3.0	4.8 ± 2.5	3.9 ± 2.3
Psychological disability[d]	2.6 ± 1.2	3.0 ± 1.3	207.5 / 0.255	0.255	2.8 ± 1.2	2.9 ± 1.4	197.0 / 0.600	2.4 ± 0.9	2.8 ± 1.1	2.9 ± 1.3
Social disability[d]	2.4 ± 0.9	3.3 ± 1.6	170.5 / 0.030*	0.030*	2.8 ± 1.3	2.9 ± 1.5	209.5 / 0.824	2.8 ± 1.8	2.9 ± 1.3	2.8 ± 1.4
Handicap[d]	2.6 ± 1.1	3.3 ± 1.7	189.5 / 0.106	0.106	2.9 ± 1.5	3.0 ± 1.6	208.0 / 0.818	3.8 ± 3.0	3.2 ± 1.3	2.6 ± 1.1

- aMann-Whitney U-test.
- bKruskal-Wallis H-test.
- p-value considered significant at < 0.05 (2-tailed).
- Higher scores (EORTC: max 100, OHIP: max 10) represent improved quality of life (fewer symptoms).
- Higher scores (EORTC: max 100, OHIP: max 10) indicate poorer quality of life (more symptoms).

Oral pain was the most commonly reported issue on the OHIP-14 questionnaire **(Table 7)**. Social disability, as assessed by the OHIP-14, was significantly higher among patients with oral mucosal cGvHD compared to those without these symptoms (Mann–Whitney U-test, p = 0.030).

The goal of this study was to explore the prevalence, nature, and severity of taste and smell alterations in individuals with oral cGvHD and to investigate whether these sensory changes are associated with oral mucosal cGvHD manifestations, salivary flow, and both global and oral health-related quality of life (OH-QoL).

We found that 68.9% of participants had reduced taste perception, although not all of these patients recognized this change. On the other hand, 40% experienced smell disorders, including 28.9% with hyposmia (reduced smell) and 11.1% with anosmia (complete loss of smell). Interestingly, most individuals with hyposmia or anosmia also reported a reduction in their smell perception. The presence of taste and smell disturbances was roughly similar between those with and without visible oral mucosal cGvHD symptoms, which aligns with earlier findings [4]. Additionally, no clear connection was found between salivary flow levels and taste perception. Both taste and smell impairments did not appear to significantly affect the participants' overall or oral health-related quality of life.

The rate of hypogeusia in this study (68.9%) is similar to the 66.6% found in a study by Ferreira *et al*. which focused on the neutropenic period following HSCT [29]. Our research, however, included participants who were evaluated at least 100 days post-transplant, suggesting that the sensory disturbances can persist well beyond the neutropenic phase. While it's known that patient-reported taste issues may fade within 3 years after HSCT [4, 9], some of the patients in this study reported taste disturbances that lasted from 3 months to over 10 years after the transplant. Notably, some individuals with objectively reduced taste sensitivity were not aware of the impairment, potentially indicating an adaptation to the condition over time.

Given the short lifespan of taste and smell receptor cells (7 to 10 days), they are particularly vulnerable to the toxic effects of the conditioning regimen, which often includes chemotherapy and/or radiotherapy [30, 31]. However, taste disturbances due to radiation are typically observed only with higher doses (over 20 Gy) targeted at the head and neck region. Since the maximum dose of total body irradiation received by our participants was 10 Gy, the impact of radiation on taste and smell disturbances in our study is likely negligible.

Interestingly, the bitter taste was one of the most preserved sensations in our study. This may be due to its evolutionary role in detecting potentially harmful substances [32]. Chemotherapy agents like cyclophosphamide may interfere with taste sensation pathways, leading to altered taste perceptions even in the absence of corresponding flavor molecules [31, 33]. Moreover, common medications such as antimicrobials, corticosteroids, and psychoactive drugs can negatively affect taste and smell, either by reducing sensory function or causing perceptual distortions due to neurotoxicity [34]. Due to the wide variety of medications used by our participants (more than 100 different drugs), we could not pinpoint the exact impact of each on taste and smell.

All patients included in this study had either current or past oral manifestations of mucosal cGvHD. Oral mucosal manifestations of cGvHD can vary greatly over time due to a combination of factors, such as therapeutic influences (e.g., immunosuppressive treatments) and patient-related factors (e.g., infections, stress, and treatment adherence). In our study, most mucosal manifestations were mild to moderate in severity. As both we and other researchers have observed, patients often report persistent oral

symptoms related to cGvHD even in the absence of visible signs [35, 36]. Additionally, as reported by Sato *et al*. self-reported oral cGvHD symptoms are a strong predictor of taste disorders in patients who are more than 3 months post-transplant [9].

cGvHD can also affect salivary glands, leading to reduced saliva production (hyposalivation), which can impair taste perception. Changes in the biochemical and immunological composition of saliva are commonly linked to reduced salivary function after alloHSCT, and this can negatively impact both taste and oral health [37]. However, our study did not find a significant relationship between hyposalivation and taste or smell disturbances. Larger and more comprehensive studies are necessary to further explore this potential connection.

Scordo *et al*. examined research focusing on taste changes after HSCT and explored possible pathobiological mechanisms behind these alterations [38]. While inflammation related to GvHD can damage the cells and tissues involved in taste and smell perception, the exact relationship between chronic GvHD (cGvHD) and sensory dysfunction remains unclear. To better understand the origins and mechanisms behind these sensory issues, a comprehensive approach should be considered, targeting potential cellular pathways and mechanisms that affect multiple organs, such as the oral and nasal epithelium, lungs, kidneys, and liver in cGvHD patients. Additionally, recent investigations into taste and smell disorders linked to COVID-19 may offer valuable insights into the mechanisms involved. Interestingly, research suggests that the renin-angiotensin system plays a critical role in taste sensitivity modulation, warranting further research in this area [39].

Taste and smell are key drivers in food choices. However, eating is also a significant aspect of social, cultural, and familial life. Consequently, alterations in taste and smell can lead to not only nutritional issues and weight loss but also reduced social interactions, negatively affecting quality of life (QoL) [6]. This study observed a decline in oral health-related QoL, though no significant differences were found between patients with or without taste and smell disorders using the EORTC-15 and OHIP-14. In general, patients with GvHD appeared to adapt their lifestyles to their health challenges and expressed acceptance of their post-transplant lives, despite reporting a negative impact on their social interactions. However, this study focused solely on oral cGvHD and did not consider other body sites or coexisting conditions that may have further impacted overall QoL.

Currently, there are limited supportive care options available to alleviate taste disorders, with only minimal evidence supporting their effectiveness. Interventions such as dietary counseling, amifostine, zinc supplementation, and photobiomodulation have been proposed as possible treatments [31, 40, 41]. Therefore, it is crucial to develop more effective strategies for preventing and managing these issues in patients.

Overall, the findings suggest a high incidence of hypogeusia, with smell disturbances being less common but still a significant clinical concern. Future research is needed to deepen our understanding of the prevalence and mechanisms of taste and smell dysfunctions, and their impact on both physical and mental health. Long-term studies are necessary, involving larger patient groups stratified by factors such as age, gender, oral health, cancer treatment history, stem cell source, and the presence of oral or non-oral cGvHD, to assess patterns and potential risk factors for taste and smell disturbances. Given the reduced ability to taste umami, testing should also focus on this flavor [9]. Additionally, systematically evaluating taste and smell abilities could raise awareness of these issues among healthcare providers and underscore the need for specialized supportive care strategies tailored to individual patient needs.

Conclusion

Taste and smell disturbances are prevalent among alloHSCT recipients, even long after the transplant. While many patients report diminished oral health-related QoL, the precise impact of taste and smell impairments on their quality of life remains to be fully understood.

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