Gustatory dysfunction in patients with olfactory dysfunction and the associated factors*

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Abstract

Background: Little is known about the occurrence of gustatory dysfunction (GD) in relation to different aetiologies of olfactory dysfunction (OD) as assessed by psychophysical chemosensory tests. The aim of this study was to analyse gustatory function in patients with OD and to investigate clinical factors associated with GD.

Methods: A total of 742 individuals who underwent both olfactory and gustatory function tests at a tertiary medical centre from November 2019 to March 2021 were retrospectively enrolled. Olfactory and gustatory function were assessed by the YSK olfactory and gustatory function tests, respectively. Patients with OD were classified into four groups according to the aetiology: sinonasal disease, post-infection OD (PIOD), post-traumatic OD (PTOD), and others. Secondary outcomes included age, sex, smoking history, and alcohol history.

Results: Among the 488 patients with OD, 93 (19.1%) showed GD and 395 (80.9%) had normal gustatory function. Only 25 (9.8%) among 254 individuals with normosmia showed GD. Analyses of these frequencies revealed a significant association between OD and GD. In addition, the taste score was significantly lower in patients with OD than individuals with normosmia. The frequency of GD was significantly higher in patients with PTOD (53.6%) than in those with OD of other aetiologies (sinonasal disease, 6.7%; PIOD, 13.0%; others, 24.4%). In the multivariate analysis, age ≥55 years and PTOD were associated with a high frequency of GD among patients with OD.

Conclusions: The current study show that GD is significantly associated with OD. In particular, GD is more common in patients with PTOD than in those with OD of other aetiologies.

Key words: gustation, olfaction, smell, taste

Introduction

Special senses, including vision, hearing, equilibrium, olfaction, and gustation, are essential to human life. Of these, olfaction and gustation are chemical senses that are initiated by the binding of molecules that are smelled or tasted to their receptors [1,2]. Olfaction and gustation play a crucial role in food selection, nutrition, and the awareness of hazardous materials, such as spoiled food, toxic gases, and fires [3,4]. Disturbances in olfaction and gustation are associated with poorer quality of life and higher risk of mortality [4,5].

Although olfaction and gustation are mediated by different receptors in anatomically distinct locations, the olfactory and gustatory systems are concomitantly activated during eating, and these senses are interconnected. Several studies reported that olfaction influences taste perceptions [6-8]. Conversely, olfaction is also affected by gustation [9]. A considerable proportion of what we think of as gustation is derived from the stimulation of olfactory receptors via retronasal olfaction. In particular, the

identification of flavour is known to be mediated jointly by olfaction, taste, and trigeminal stimulation [10-12]. In line with this, the majority of previous studies [3,13,14], but not all studies [15], that conducted both olfactory and gustatory function tests showed a significant association between olfactory dysfunction (OD) and gustatory dysfunction (GD). Therefore, cross-modal interaction between olfaction and gustation needs to be considered in the management of patients with OD. Patients often complaint not only about smell, but also taste loss. However, most of them present olfactory dysfunction only because a major component of taste, called aromas, is mediated by retronasal olfaction, which is dysfunctional as well. The confusion between smell and taste during history taking, and the fact that OD patients may be unaware of simultaneous impairment in gustatory function (e.g. post-viral infection) may motivate clinician to assess taste function with psychophysical tests to better localize the problem, especially in the context of medico-legal or insurance issues [16]. Thus, clarification of when a test for gustatory function should be performed in patients who present for olfactory loss is needed. However, clinical factors associated with GD in patients with OD remain unclear. Furthermore, little is known about the frequency of GD across different aetiologies of OD as assessed by psychophysical chemosensory tests.

In the present study, we retrospectively investigated the association between GD and OD in individuals who had undergone both olfactory and gustatory function tests. We aimed to examine the frequency of GD according to the aetiology of OD and to investigate clinical factors associated with GD in patients with OD.

Materials and methods

Study subjects

In the current study, 742 individuals who underwent both olfactory and gustatory function tests due to preoperative evaluation or subjective OD and/or GD at the Severance Hospital, Republic of Korea, from November 2019 to March 2021, were retrospectively enrolled. This study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (IRB No. 4-2021-0770). All procedures involving human participants were performed according to the principles of the Declaration of Helsinki. Information about age, sex, smoking history, alcohol history, and results of the olfactory and gustatory function tests were collected from medical records.

We classified the patients with OD into four groups according to the aetiology: sinonasal disease, post-infection OD (PIOD), post-traumatic OD (PTOD), and others. Patients who had undergone sinonasal surgery (endoscopic sinus surgery, septoplasty, or tumor resection) for treatment of sinonasal pathologies, including chronic rhinosinusitis (CRS), septal deviation (SD), and sinonasal tumor, without a history of head trauma and recent upper respiratory infection were included in the sinonasal disease group. Patients with a recent history of upper respiratory infection and subsequent OD were considered as the PIOD group. Patients who exhibited OD following head trauma were included in the PTOD group. The remaining patients were included in the group, referred to as "others". The aetiologies of the "others" group were congenital, neurodegenerative diseases, and idiopathic.

Olfactory function test

Olfactory function was evaluated using the YSK olfactory function test (YOF test, Kimex Co., Suwon, Korea) as previously reported [17]. Briefly, all odorants were provided in felt-tip pens. The test procedure required covering the subject's eyes, placing the pens 2 cm away from the subject's nostrils, and smelling each pen for 3 seconds. All test procedures were performed in a room equipped with an air ventilation hood. The YOF test is composed of three tests for odour threshold (T), odour discrimination (D), and odour identification (I). The identification test included eight universal and four Korean culture-friendly odorants. The score ranges of the YOF subtests were 1–12 for the threshold test, 0–12 for the discrimination and identification tests, and 1–36 for the total TDI score. The TDI score was calculated as the sum of the T, D, and I scores. The diagnostic cut-off of the TDI score was ≤14.5 for anosmia and 14.5 <TDI score ≤21.0 for hyposmia [17]. OD refers to both hyposmia and anosmia.

Gustatory function test

Gustatory function was examined using the YSK gustatory function test (RHICO Medical Co., Seoul, Korea) [18]. Liquid solutions were used for the gustatory function assessment. The test consisted of 30 taste solutions (six concentrations of five tastants: sweet [sucrose], bitter [quinine hydrochloride], salty [sodium chloride], sour [citric acid], and umami [monosodium glutamate]). The solution with the highest concentration of each tastant was scored as 1, and the solution with the lowest concentration was scored as 6. Distilled water was used as the solvent. The taste score was defined as the sum of the recognition thresholds. Based on the standard of GD as described in a previous publication [18], patients with taste scores <12 were considered to have GD.

Statistical analysis

SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8 (GraphPad Software Inc., San Diego, CA, USA) were used for statistical analyses. Statistical significance was set at $P < 0.05$. Comparisons between categorical variables were evaluated using the Chi-square test or Fisher's exact test with Bonferroni correction. Unpaired t-tests were used to compare continuous variables between the two unpaired groups. One-way ANOVA with Tukey's multiple comparisons test or the Kruskal-Wallis test with Dunn's multiple comparison test was used to compare data between multiple groups. Multivariate analysis

Table 1. Characteristics of different subgroups of patients with OD.

Parameter	Sinonasal disease (n=355)	PIOD (n=23)	PTOD (n=28)	Others (n=82)
Age, years[§,a]	53 (28)	60 (16)	42.5 (24.5)	59 (19.25)
Gender (F/M)[b]	137/218	18/5*	8/20[‡]	47/35
Smoking Hx, n (%)[b]	125 (35.2%)	5 (21.7%)	17 (60.7%)[†,‡,#]	25 (30.5%)
Alcohol Hx, n (%)[b]	130 (35.9%)	4 (17.4%)	14 (50%)	27 (32.9%)
Anosmia, n (%)[b]	166 (46.8%)	15 (65.2%)	23 (82.1%)[†,#]	42 (51.2%)
Gustatory dysfunction, n (%)[b]	55 (6.7%)	3 (13.0%)	15 (53.6%)[†,‡,#]	20 (24.4%)
Parosmia, n (%)[c]	10 (4.7%)	4 (17.4%)*	2 (7.1%)	7 (8.5%)

OD, olfactory dysfunction; PIOD, post-infection olfactory dysfunction; PTOD, post-traumatic olfactory dysfunction; F, female; M, male; Hx, history; §Data are presented as median (interquartile range). [a] Statistical analyses were performed using the Kruskal-Wallis test with Dunn's multiple comparison test. [b] Statistical analyses were performed using the Chi-square test with Bonferroni correction. [c] Statistical analyses were performed using the Fisher's exact test with Bonferroni correction. *Statistically significant difference between the PIOD group and the sinonasal disease group, adjusted P<0.05. [†]Statistically significant difference between the PTOD group and the sinonasal disease group, adjusted P<0.05. [‡] Statistically significant difference between the PTOD and PIOD groups, adjusted P<0.05. [#] Statistically significant difference between the PTOD group and the other group, adjusted P<0.05.

using logistic regression was performed on the variables that showed a P value <0.05 in the univariate analysis.

Results

Baseline characteristics of total study subjects

A total of 742 individuals (424 men and 318 women) were included in the study. The median age of total study subjects was 55 years (range, 9–87 years). Of these, 337 (45.4%) and 48 (6.5%) individuals had self-reported OD and GD, respectively. In olfactory function test, 254 (34.2%) individuals showed normal olfactory function (normosmia) and 488 (65.8%) had OD (hyposmia/anosmia). In addition, 118 (15.9%) individuals had GD according to the gustatory function test.

Association between olfactory dysfunction and gustatory dysfunction

Among the 488 patients with OD, 93 (19.1%) had GD and 395 (80.9%) had normal gustatory function (normogeusia). Only 25 (9.8%) among 254 individuals with normosmia showed GD, while the other 229 (90.2%) had normogeusia. Analysis of these frequencies revealed that OD was significantly associated with GD (chi-square test, P=0.001). We also found that the taste score was significantly lower in patients with OD than in individuals with normosmia (16.2±5.1 vs. 17.5±4.3, P<0.001; Figure 1A). On the other hand, there was no significant difference in the taste score between patients with hyposmia and those with anosmia (16.1±4.8 vs. 16.2±5.3, P=0.985; Figure 1B). In the subgroup analysis according to the five different tastes, significant differences in the taste score between patients with OD and individuals with normosmia were observed for sweet (normosmia vs. OD, 4.4±1.2 vs. 4.1±1.5; P=0.003), salty (2.9±1.2 vs. 2.6±1.4; P=0.003), and bitter (3.6±1.0 vs. 3.2±1.2; P<0.001) tastes, but not for sour (2.8±1.6 vs 2.7±1.7; P=0.247) and umami taste (3.8±1.9 vs 3.6±2.0; P=0.084).

Frequency of gustatory dysfunction according to the aetiology of olfactory dysfunction

Among all the patients with OD (n=488), 242 (49.6%) had hyposmia and 246 (50.4%) had anosmia. There were 278 men and 210 women. The median age was 55 years (range, 9–87 years). The aetiology of OD was identified as sinonasal disease (n=355, 72.7%), URI (n=23, 4.7%), head trauma (n=28, 5.7%), or miscellaneous causes (n=82, 16.8%).

To investigate whether the prevalence of GD differs according to the aetiology of OD, we divided the patients with OD into four groups: sinonasal disease, post-infection OD (PIOD), post-traumatic OD (PTOD), and others (Table 1). The proportion of GD was significantly higher in the PTOD group (53.6%) compared with the other groups (sinonasal disease, 6.7%; PIOD, 13.0%; others, 24.4%) (P<0.05 for each comparison; Table 1). The proportion of anosmia was also significantly higher in the PTOD group (82.1%) compared to the sinonasal disease group (46.8%) or the "others" group (51.2%) (P<0.05 for each comparison; Table 1). Age was not significantly different between the PTOD group and the other groups (P>0.05 for each comparison; Table 1). When we compared taste scores between the OD groups, the PTOD group (12.1±8.0) showed significantly lower taste scores than the others (sinonasal disease, 16.5±4.5; PIOD, 17.1±4.0; others, 15.8±5.6) (P<0.01 for each comparison; Figure 2A). TDI scores were significantly lower in the PTOD group (10.4±4.5) than in

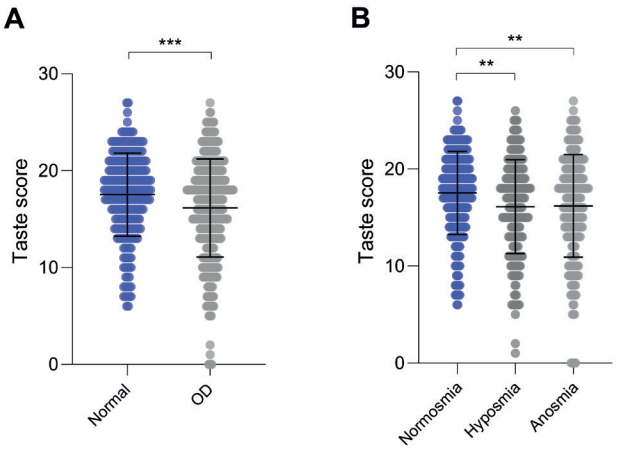

Figure 1. Comparison of the taste score between patients with normosmia and those with olfactory dysfunction. (A) Taste scores of patients with normosmia (n=254) and those with OD (n=488). (B) Taste scores of the normosmia (n=254), hyposmia (n=242), and anosmia (n=246) groups. Data are presented as mean and standard deviation (SD). **P<0.01, ***P<0.001. OD, olfactory dysfunction.

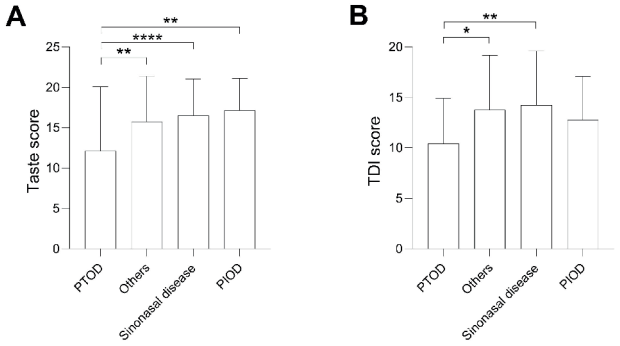

Figure 2. Taste and TDI scores according to the aetiology of olfactory dysfunction. Taste score (A) and TDI score (B) were compared between patients with sinonasal disease (n=355), post-infection OD (PIOD; n=23), post-traumatic OD (PTOD; n=28), and others (n=82). Data are presented as mean and SD. *P<0.05, **P<0.01, ****P<0.0001.

the sinonasal disease (14.1±5.3) and others (13.8±5.4) groups (P<0.05 for each comparison), whereas scores were not different between the PTOD and PIOD (12.8±4.3) groups (Figure 2B).

Clinical factors associated with gustatory dysfunction in patients with olfactory dysfunction

Finally, we investigated the association between clinical factors and GD in patients with OD (Table 2). Clinical factors included age, sex, smoking history, alcohol history, degree of OD, aetiology of OD, and the presence of parosmia (Table 2). As the PTOD group showed a significantly higher prevalence of GD than the other groups in Table 1, we classified the aetiology of OD as "PTOD" and "non-trauma" in this analysis. The univariate analysis revealed that age ≥55 years (P<0.001), male sex (P=0.002), smoking history (P=0.001), and PTOD (P<0.002) were significantly associated with a high prevalence of GD (Table 2). In the multivariate analysis, age ≥55 years (adjusted OR 2.320, P=0.016) and PTOD (adjusted OR 2.264, P<0.001) were identified as the independent factors associated with a high frequency of GD (Table 2). In contrast, sex (P=0.521) and smoking history (P=0.355) were not associated with a high frequency of GD (Table 2).

Discussion

In the present study, we observed a significant association between OD and GD. Furthermore, we found that old age and PTOD were significantly associated with a high frequency of GD in patients with OD. These data show a close link between olfaction and gustation on the basis of function test results and add new knowledge regarding clinical factors associated with GD in patients with OD. Moreover, the current findings suggest that olfaction and gustation may not compensate for each other, but rather decrease simultaneously.

Accumulating evidence has suggested a mutual interaction between olfaction and gustation. Taste qualities enhance the fruitiness olfactory intensity perceived orthonasally [19]. Caramel odour enhances sweetness but decreases sourness [8]. Similarly, strawberry odour tends to intensify sweetness [6]. A previous study using taste strips reported that the taste score was lower in subjects with impaired olfaction than those with normal olfactory function [13], which is similar to the current results. In that study, the frequency of GD was reported to be more than 40% (45/107) among patients with OD, which is higher than our results (19%). This discrepancy may be due to differences in the gustatory function tests used.

The primary signalling pathways of olfaction and gustation are distinct. The binding of odorants to olfactory receptors in the olfactory epithelium generates electrical impulses [20]. These signals are transmitted to the olfactory bulb via the olfactory nerve and ultimately, to the primary olfactory cortex and orbitofrontal cortex [20]. The gustatory signalling begins with the detection of tastants by taste bud cells in the tongue. Generated signals are then transmitted by the chorda tympani, glossopharyngeal, and the vagus nerve to the nucleus solitarius, thalamus, and finally the primary gustatory cortex [21]. On the other hand, connections between olfactory and gustatory signalling pathways have also been reported. These two pathways are known to converge at the orbitofrontal cortex, referred to as the secondary olfactory and gustatory cortex [22]. Stroke patients with lesions of the orbitofrontal cortex tend to exhibit more frequent taste alterations than stroke patients with other lesions [23]. Moreover, several studies have reported that both olfactory and taste receptors are expressed in various peripheral tissues [24-27]. A recent study showed that functional olfactory receptors are present in cultured fungiform taste papilla cells [28], suggesting that the interaction

Table 2. Association between clinical factors and gustatory dysfunction in patients with OD.

Clinical factors	Gustatory dysfunction, n (%)		P value[a]	Multivariate analysis[b]	P value
	Absent	Present		Adjusted OR (95% CI)	
Total no.	395	93	NA	NA	NA
Age[c]					
<55	213	30		Ref	NA
≥55	182	63	<0.001	2.320 (1.426-3.774)	0.001
Sex					
Female	183	27		Ref	NA
Male	212	66	0.002	0.659 (0.184-2.356)	0.521
Smoking Hx.					
(-)	269	47		Ref	NA
(+)	126	46	0.001	1.300 (0.745-2.269)	0.355
Alcohol Hx.					
(-)	251	62			
(+)	144	31	0.572	NA	NA
Degree of OD					
Hyposmia	194	48			
Anosmia	201	45	0.665	NA	NA
Aetiology					
Non-trauma	382	78		Ref	NA
PTOD	13	15	<0.001	2.264 (1.520-3.372)	<0.001
Parosmia					
(-)	379	86			
(+)	16	7	0.173	NA	NA

Hx, history; OD, olfactory dysfunction; PTOD, post-traumatic olfactory dysfunction; NA, not available; [a] Univariate analyses were performed using the Chi-square test or Fisher's exact test. [b] Variables with P<0.05 in the univariate analysis were included in the multivariate analysis. [c] Patients were divided into two subgroups based on the median age (55 years old) of the total patients.

between olfaction and gustation may occur at the taste receptor cells in the periphery.

In the current study, we found no significant difference in the taste score between the anosmia group and hyposmia group. These results suggest that the magnitude of OD is not the sole determinant for gustatory function despite a significant association between OD and GD. Moreover, the degrees of OD and GD may depend on the location of the lesion: For instance, gustation may be more greatly affected than olfaction in conditions predominantly affecting peripheral gustatory signalling pathways, such as tongue diseases. Conversely, sinonasal diseases blocking the olfactory cleft may cause OD, but rarely GD. Interestingly, no significant difference in sour and umami taste scores was observed between patients with OD and those with normosmia, suggesting that the olfaction-gustation interaction may be affected by the tastant type. Given that taste bud cells can be subgrouped into four types that detect different types of taste [29], it would be of interest to examine whether the olfaction-gustation interaction differs according to the type of taste bud cells in future studies.

Although the underlying mechanism is still unclear, PIOD is a well-known cause of olfactory loss [3]. On the other hand, GD following viral infection has been relatively less investigated. In the present study, we found that 13% of patients with PIOD showed GD. Recently, a series of studies reported a high prevalence of GD in patients with coronavirus disease 2019 (COVID-19) [30-32], a pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 infection. However, the results from most studies were based on self-reported gustatory outcomes. In addition, long-term outcomes after viral infection are still

limited. Therefore, further studies would be required to clarify the association between viral infections and GD. Furthermore, prognostic factors for post-infection GD needs to be studied in future studies. Remarkably, we observed that only 6.7% of patients with sinonasal disease-related OD showed GD. These results may be due to the fact that the majority of sinonasal diseases induce conductive OD by blocking the olfactory cleft but may not hinder the signalling pathways of taste perception. In the multivariate analysis, we found that head trauma was significantly associated with a high prevalence of GD in patients with OD. In line with a previous study [3], we also observed that the frequencies of anosmia and GD were higher in the PTOD group than in the other OD groups. These results suggest that both olfaction and gustation should be assessed in patients with head trauma. Damage at both the peripheral and central sites may lead to post-traumatic GD. In particular, the chorda tympani nerve responsible for taste perception from the anterior two-thirds of the tongue is vulnerable to head trauma due to its long extracranial route [33]. Traumatic brain lesions at the site that is associated with both olfactory and gustatory signalling pathways, such as the orbitofrontal cortex, may also result in the co-occurrence of GD and OD. Further studies are needed to investigate whether the GD is dependent on the location of traumatic lesions in patients with PTOD. Old age was also an independent factor for GD among patients with OD. However, considering that the perception of taste decreases with normal aging [18,34], interpretation of the results should be cautious and additional studies are needed to verify the results.

The limitation of this study includes the inherent features of retrospective studies. Since the considerable proportion of enrolled patients underwent olfactory function tests due to preoperative evaluation, we cannot rule out the possibility of selection bias. In addition, trigeminal function, another major sense contributing to chemosensory perception, was not assessed in this study. Given the known associations for trigeminal sensation with olfaction and gustation [35-38], it seems plausible that trigeminal function may affect the frequency of GD in patients with OD. Although a recent study reported that the cause of OD exerted no effect on trigeminal scores [14], further studies are warranted to investigate the effect of trigeminal function on gustation in relation to aetiologies of OD. Despite these limitations, this study does have several strengths. First, we enrolled a large number of subjects who underwent validated function tests for both olfaction and gustation. Second, we compared the prevalence of GD according to the aetiology of OD. Third, our study investigated the clinical factors associated with GD in patients with OD.

Conclusion

In summary, our results showed that GD is significantly associated with OD. In particular, old age and PTOD were significantly associated with a high prevalence of GD. These findings strongly suggest that gustatory function should be assessed in patients with OD, particularly those with a history of head trauma. In this regard, our current analysis could hold important implications to medico-legal problems among patients with OD and provides valuable information for a better understanding of the interaction between olfaction and gustation.

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Authorship contribution

M-SR: conceptualization, analysis, and writing; H-JC: analysis and editing; J-HY: conceptualization and review; SJM: conceptualization and review; C-HK: conceptualization, editing, and review.

Conflict of interest

The authors declare that no conflict of interest exists.

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