ORIGINAL

Umami taste sensitivity is associated with food intake and oral environment in subjects with diabetes

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Abstract : Objective : Dysgeusia is a serious problem in patients with diabetes because it often leads to overeating, which is associated with disease progression. This study aimed to investigate the association between taste sensitivity, eating habits, and the oral environment. Subjects and methods : In this cross-sectional study of 75 subjects with diabetes, gustatory function was assessed using the whole-mouth method, and lingual taste receptor gene expression was measured by real-time PCR. Food intake was evaluated using a food frequency questionnaire based on food groups. The oral environment was assessed using xerostomia and periodontal comprehensive examination. Results : In total, 45.3%, 28.0%, and 18.7% of subjects showed lower umami taste sensitivity, low sweet taste sensitivity, and low salt taste sensitivity, respectively. Lower umami sensitivity correlated with lower estimated glomerular filtration rate and higher energy-source food intake. Subjects with diabetes with higher plaque control record showed significantly higher T1R3 gene expression than those with lower plaque control record. Conclusion : Reduced umami taste sensitivity is associated with decreased renal function and high energy food intake in diabetes. Subjects with diabetes with higher plaque control record showed significantly higher T1R3 gene expression, suggesting that the oral environment affects taste gene expression. J. Med. Invest. 70 : 241-250, February, 2023

Keywords **:** *Umami, taste sensitivity, Diabetes, Food intake, Oral environments*

INTRODUCTION

Dysgeusia is a serious problem that can lead to malnutrition and decreased quality of life (QOL). According to the 2019 clinical survey on subjects with taste disorders in Japan, the prevalence of taste disorders was twice as high as that in the 1990 survey (1). However, to date, there is no established supportive care method due to the complexity of the cause and lack of evidence.

Dysgeusia is caused by several factors such as zinc deficiency (2), drug use (3), oral dryness (4), metabolic disorders including diabetes (5, 6), chronic kidney disease (CKD) (7), hypertension (8), psychogenic disorders (9), chemotherapy (10), aging (11), and coronavirus disease 2019 (COVID-19) infection (12). Usually, dysgeusia decreases appetite ; however, in subjects with diabetes, it frequently leads to overeating and changes in eating behavior, accelerating the progression of diabetic pathology. Notably, these taste disorders that induce overeating in subjects during unconsciousness, without interventions such as nutritional counseling, can exacerbate obesity and poor glycemic control, even while under drug treatment.

Subjects with diabetes have also been reported to have oral cavity diseases such as dental caries, tongue coating, xerostomia, periodontal disease, and candida infection (13), and the progression of periodontitis is known to exacerbate glycemic control (14, 15). Aemaimanan *et al*. reported that increased levels of *Porphyromonas gingivalis*, a periodontal pathogen, in subjects with type 2 diabetes mellitus were positively correlated with hemoglobin A1c (HbA1c) levels (16). However, the oral environment has not been given much emphasis as a risk factor for dysgeusia in subjects with diabetes, except for oral dryness, and there are few reports on the association between periodontal disease and dysgeusia.

We previously reported that lingual taste receptor gene expression decreases during chemotherapy in patients with head and neck cancer (10). Lingual taste receptors are stimulated by the taste of substances such as monosodium glutamate (MSG), thereby increasing taste receptor gene expression (17, 18). However, we recently reported that the taste receptors of subjects with diabetes are expressed differently from those of the general population, suggesting overexpression due to overeating in the patients (19).

Umami is one of the 5 basic taste and several studies have reported low umami taste sensitivity in individuals with obesity (20, 21). These reports led us to hypothesize that : 1) low taste sensitivity may lead to overeating, which in turn leads to poor glycemic control, and 2) exacerbation of the oral environment, which is closely related to poor glycemic control, may cause further loss of taste function, which in turn leads to overeating. Therefore, the present study was designed to examine the close relationship between dysgeusia, eating behavior, oral environment, and glycemic control in diabetes.

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SUBJECTS AND METHOD

Study design and subjects

This cross-sectional study was approved by the ethics committee of the Tokushima University Hospital (approval no : 4066).

Informed consent was obtained from 82 outpatients with diabetes in the Department of Endocrinology and Metabolism (Tokushima University Hospital) between November 2021 and May 2022. Among the 82 subjects, seven were excluded from the study, and the remaining 75 subjects were included for data analysis. In addition periodontal comprehensive examination was performed in 69 subjects, excluding subjects with edentulous jaw and those who refused the examination (Figure 1). We collected clinical information (body mass index [BMI], diabetes duration, HbA1c, and estimated glomerular filtration rate [eGFR]) from medical records in the hospital. Twenty-two healthy individuals were recruited as the control group (mean age : 54.4 ± 17.3 years, 14 males, 8 females).

Gustatory test

Gustatory function was assessed using the whole-mouth method. We prepared umami solutions (0.048%, 0.095%, 0.191%, 0.382%, and 0.763% L[+]-glutamic acid monosodium salt monohydrate, Nacalai Tesque Inc. Kyoto Japan), sucrose solutions (0.156%, 0.313%, 0.625%, 1.25%, and 2.50% sucrose, Hayashi Pure Chemical, Ind., Ltd., Osaka Japan), and salt solutions (0.0391%, 0.0781%, 0.156%, 0.313%, and 0.625% sodium chloride, Hayashi Pure Chemical, Ind., Ltd.), based on a previous report (22). Briefly, 1 ml of each taste solution was applied to the tongue until taste recognition. The participants chose one of the following seven possible answers : sweet, salty, umami, sour, bitter, unidentifiable, or no taste. To avoid accidental correct responses, the test was repeated until two consecutive correct answers were recorded, and the first concentration provided was set as the cognitive threshold. The subjects were asked to avoid eating and drinking anything except water two hours before the test. For sweet and salt, the cutoff value for low taste sensitivity was set based on a previous study (23). Since there was no cutoff value defined for umami taste, the median cognitive threshold was used as the cutoff value, and those exceeding the median were defined as the low umami sensitivity group.

Assessment of xerostomia

Xerostomia (dry mouth) was assessed using an oral moisture-checking device (Mucus®, Life Co., Saitama, Japan) based on a previous study (24, 25) ; the device can measure the amount of moisture in the oral cavity. The cover was attached to the measuring section at the tip of the device and pressed vertically 10 mm from the tip of the tongue. We repeated the measurement for three consecutive times, used the median as a representative value (24), and defined a score ≤ 27.9 as "dry mouth".

Periodontal comprehensive examination

Dentists specializing in periodontal disease assessed number of teeth, bleeding on probing (BOP), plaque control record (PCR), pocket probing depth (PPD) and periodontal inflamed surface area (PISA). The cut-off value for PCR was > 20%, as reported by Mameno *et al*. (26). We measured six points of the teeth to assess PPD and calculated the percentage of teeth with PPD ≥ 4 mm to indicate moderate periodontitis and 6 mm to indicate severe periodontitis. The severity of periodontitis was determined according to a guideline (27) and a previous report (28). However, we did not measure clinical attachment loss due to the lack of data in this study. PISA, which quantifies the amount of inflamed periodontal tissue, was calculated using BOP and PPD (29), and it has been reported to be associated with C-reactive protein (30) and HbA1c levels in subjects with type 2 diabetes (31).

Analysis of taste receptor gene expression level

We measured the mRNA expression of taste receptor type 1 member 1 [T1R1] and taste receptor type 1 member 3 [T1R3], which were subunits of umami taste receptor (17), using the lingual foliate papillae of subjects with diabetes (19). The lingual foliate papillae of the subjects were scraped from a screw cap and stored in 2 ml serum tubes (Sumitomo Bakalite, Tokyo, Japan) containing RNA later® (Ambion, Austin TX, USA) at -80℃ as a sample. Total RNA was extracted from samples using the RNA Queous® Kit (Ambion), and cDNA was amplified using the CellAmp® Whole Transcriptome Amplification Kit (Takara Bio, Shiga, Japan) according to the manufacturer's protocol. Real-time PCR was performed using SYBR Green and StepOnePlus real time PCR system (Life Technologies, Carlsbad, CA, USA) under the following conditions : initial PCR activation, 95℃ for 20 s, followed by 40 cycles at 95 ℃ for 3 s and 60 ℃ for 30 s PCR, ending with a melt curve stage at 95℃ for 15 s, 60℃ for 1 min, and 95℃ for 15 s. The relative amounts of mRNA were normalized to GAPDH mRNA levels within each

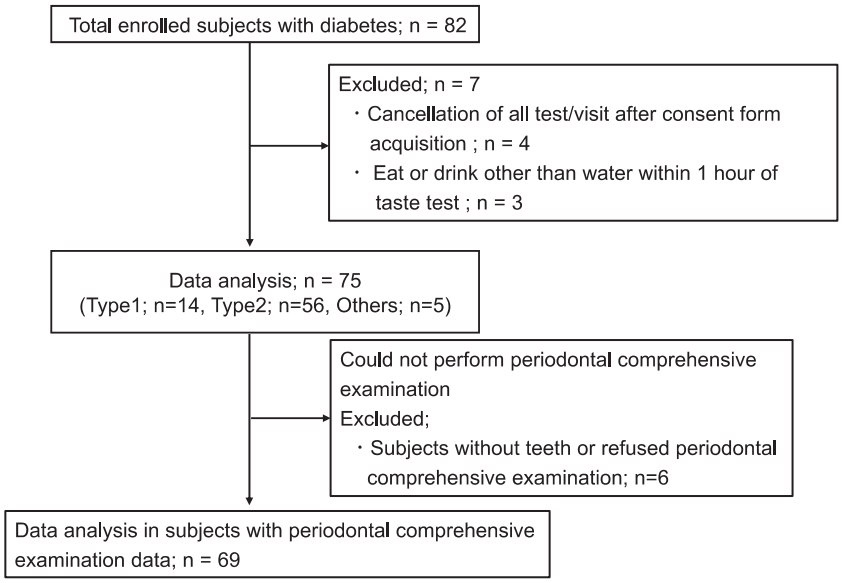

Figure 1. Inclusion criteria of the study participants

sample. The expression of mRNA was quantified using the ΔΔCT method, which is shown relative to the median expression in 22 healthy participants. The primer used is shown in Supplemental Table 1. We divided the subjects into high and low taste receptor gene expression groups according to the median relative ratio of gene expression levels.

Food intake questionnaire

Food group intake in the previous month was assessed using a food frequency questionnaire based on food groups (FFQg) Ver.6.0 (Kenpakusha Co. Ltd., Tokyo, Japan). This questionnaire has been previously described in detail (32). Food intake trends were divided into four groups : Group 1 included milk, dairy products, and eggs ; Group 2 included fish, meats, and beans or bean products ; Group 3 included vegetables, potatoes, and fruits ; and Group 4 included grain, sugar, oil, or other luxury grocery items (33). Food intake was adjusted by density and amount (g) per 1000 kcal (34).

Eating behavior and umami taste preference questionnaire

To examine eating behavior and taste preference, we used a questionnaire ; eating behavior was answered by yes/no choice or question to fill in the frequency and tastes preference was assessed by 5-Point Liker Scale ranging from "like very much (1) to "dislike" (5), and "like very much" or "like" were categorized into the strong preference group.

Statistical analysis

Sample size was estimated to be 70 based on a preliminary study ; however, 80 participants were selected to account for ineligible cases. The relative ratios for taste receptor gene expression in subjects with diabetes with and without taste disorder were used. The mean difference and standard deviation of the two groups were 0.13 and 0.19, respectively, with power set to 80% and $\alpha = 0.05$.

All statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA). Data are presented as median (interquartile range 25%, 75%) or number (%). In continuous data, we used Kruskal-Wallis test followed by the Steel-Dwass test for multi-group and Wilcoxon rank-sum test for paired-group. In categorical data, we used Fisher' s exact test or Chi-square test. Multiple logistic regression, adjusted for covariates (age and diabetes type), was used to identify factors associated with low taste sensitivity and high expression of taste receptor genes. Statistical significance was set at $P < 0.05$. In the multiple logistic regression, the median imputation method (35) was used to account for missing data (duration of diabetes[n=2], eGFR [n=3], HbA1c [n=1], and dry mouth [n=1]).

RESULTS

Characteristics of the subjects

Eighty-two subjects were enrolled in this study. After excluding seven subjects, the data of 75 subjects were finally analyzed (Figure 1). Of the 75 subjects with diabetes, 14 subjects had type 1 diabetes, 56 had type 2 diabetes, and 5 had other types (steroid diabetes, mitochondrial diabetes, or pancreatectomy). As shown in Table 1, the overall median age was 66.0 years, and there was no significant difference in age between the types of

Table 1. Characteristics of subjects with diabetes

	All (n=75)	Type1 (n=14)	Type2 (n=56)	Others (n=5)	P-value
Age (years)	66.0 (52.0 - 74.0)	53.5 (48.8 - 67.0)	69.0 (56.5 - 74.0)	66.0 (55.0 - 79.5)	0.079
Age≥65 years, n (%)	40 (53.3)	4 (28.6)	33 (58.9)	3 (60.0)	
Sex (Male), n (%)	38 (50.7)	5 (35.7)	31 (55.4)	2 (40.0)	
BMI (kg/m^2)	25.6 (23.1 - 31.2)	23.4 (22.1 - 26.1)[a]	26.7 (23.9 - 32.3)[b]	21.6 (18.8 - 24.0)[a]	0.002
BMI≥30kg/m^2 , n (%)	21 (28.0)	0 (0)	21 (37.5)	0 (0)	
Smoking statue, n (%)					
Current	7 (9.3)	4 (28.6)	3 (5.4)	0 (0)	
Former	28 (37.3)	4 (28.6)	21 (37.5)	3 (60.0)	
Never	40 (53.3)	6 (42.9)	32 (57.1)	2 (40.0)	
Duration of diabetes (years)	15.0 (9.0 - 22.5)	12.5 (9.0 - 17.5)	16.5 (8.8 - 23.0)	22.0 (10.0 - 23.0)	0.657
Missing, n (%)	2 (2.7)		2 (3.6)		
eGFR (ml/min/1.73m^2)	67.0 (53.0 - 81.0)	84.5 (69.0 - 90.0)[a]	61.5 (47.8 - 77.3)[b]	64.5 (50.8 - 77.5)	0.006
Missing, n (%)	3 (4.0)		2 (3.6)	1 (20.0)	
eGFR<60 ml/min/1.73m^2 , n (%)	29 (40.3)	1 (7.1)	26 (48.1)	2 (50.0)	
HbA1c (%)	7.3 (6.6 - 8.2)	7.7 (7.2 - 8.2)	7.1 (6.5 - 8.4)	7.4 (7.2 - 8.1)	0.264
Missing, n (%)	1 (1.3)		1 (1.3)		
Dry mouth, n (%)	49 (66.2)	8 (57.1)	37 (67.3)	4 (80.0)	
Missing, n (%)	1 (1.3)		1 (1.3)		
Periodontal comprehensive examination	**All (n=69)**	**Type1 (n=14)**	**Type2 (n=50)**	**Others (n=5)**	**P-value**
BOP (%)	13.9 (7.0 - 33.2)	9.1 (1.9 - 35.4)	15.7 (8.2 - 33.3)	10.2 (3.8 - 28.3)	0.319
PCR (%)	47.6 (26.9 - 63.4)	31.1 (13.0 - 54.4)	55.1 (28.8 - 68.8)	36.1 (27.9 - 62.2)	0.093
PCR > 20 %, n (%)	56 (81.2)	10 (71.4)	41 (82.0)	5 (100)	
PISA (mm^2)	192.9 (65.4 - 464.9)	182.0 (25.0 - 1296.6)	196.6 (115.6 - 466.4)	152.1 (49.3 - 315.3)	0.616
Proportion of teeth/mouth PPD ≥4mm (%)	59.1 (33.3 - 87.3)	48.2 (30.0 - 100)	63.0 (35.6 - 87.6)	35.3 (5.7 - 79.9)	0.427
Proportion of teeth/mouth PPD ≥6mm (%)	7.4 (0 - 25.0)	4.3 (0 - 89.2)	8.2 (0 - 26.0)	0 (0 - 18.8)	0.590
Prevalence PPD ≥6mm (%), n (%)	47 (68.1)	10 (71.4)	35 (70.0)	2 (40.0)	

Data are expressed as median (25 - 75%) or number (%). BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; BOP, Bleeding on probing; PCR, Plaque Control Record; PISA, Periodontal Inflamed Surface Area; PPD, Probing Pocket Depth
P-value were derived using Kruskal-Wallis test
Different alphabet letters show statistical difference (Steel-Dwass test)

diabetes. The median BMI in subjects with type 2 diabetes was 26.7 kg/m^2, and approximately 40% of the subjects had BMI ≥ 30 kg/m^2, which is categorized as obesity. In addition, approximately 40% of subjects had eGFR < 60 mL/min/1.73 m^2, and the overall median HbA1c level was 7.3%. Regarding smoking habits, 37.3% of the respondents had a history of smoking, but only 9.3% of them were current smokers. The characteristics of healthy participants were shown in supplemental Table 2.

Taste sensitivity assessment

We assessed taste sensitivity using the whole-mouth test. As shown in Figure 2, low umami taste sensitivity was detected in 45.3% of subjects (n=34) and 36.4% of the healthy participants. In addition, low sweet taste sensitivity was detected in 28.0% of subjects with diabetes and 27.3% of healthy participants. Regarding salt taste, 18.7% and 9.1% of subjects with diabetes and healthy participants, respectively, had low sensitivity. Only five subjects with diabetes (6.7%) had low sensitivity to all three tastes. Among subjects with low taste sensitivity, the proportion of those with low umami taste sensitivity was the highest, and the most observed relationship was that of low umami taste sensitivity with food intake, eating behavior, and oral environment. Therefore, these subjects were then divided into two groups : low umami taste sensitivity (≥ 0.763%, L-U group) and normal umami taste sensitivity (< 0.763%, N-U group). As shown in Table 2, subjects in the L-U group were significantly older, had a longer duration of diabetes, and had a lower eGFR, compared with those in the N-U group.

Relationship between umami taste sensitivity and each survey item

We compared food intake, eating behavior, umami taste preference, and oral environment (dry mouth and periodontal comprehensive examination) between the L-U and N-U groups.

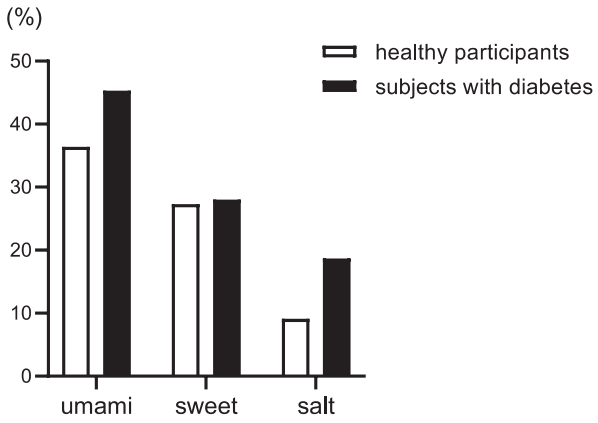

Figure 2. Percentage of subjects with diabetes and healthy participants with low umami, sweet and salt taste sensitivities
healthy participants, n = 22 ; subjects with diabetes, n = 75

As shown in Table 3, the L-U group consumed more grain/sugar/oil/other luxury grocery items, had a higher frequency of snack intake, and preferred foods with strong umami (dashi) taste. There were no differences between the groups in umami taste sensitivity and dry mouth and periodontal comprehensive examination using BOP, PCR, PISA and PPD data. We also measured the expression of lingual taste receptor genes. As shown in Figure 3, lingual T1R3 gene expression in the L-U group was significantly higher than that in the N-U group. However, there was no association between T1R1 gene expression and umami taste sensitivity.

Table 2. Comparison of characteristics between normal and low umami taste sensitivity groups

		Umami sensitivity		
		Normal (N - U group) (n=41)	Low (L - U group) (n=34)	P - value
Age (years)		62.0 (49.5 - 72.0)	70.0 (57.5 - 77.0)	0.048
Sex (Male), n (%)		19 (46.3)	19 (55.9)	0.411
BMI (kg/m^2)		26.0 (23.6 - 30.0)	24.6 (22.8 - 31.3)	0.580
Smoking statue, n (%)				
	Current	3 (7.3)	4 (11.8)	
	Former	16 (39.0)	12 (35.3)	
	Never	22 (53.7)	18 (52.9)	
Diabetes Type, n (%)				
	Type 1	10 (24.4)	4 (11.8)	
	Type 2	30 (73.2)	26 (76.5)	
	Others	1 (2.4)	4 (11.8)	
Duration of diabetes (years)		12.5 (6.3 - 20.0)	19.0 (11.0 - 26.5)	0.019
Missing, n (%)		1 (2.4)	1 (2.9)	
eGFR (ml/min/1.73m^2)		74.0 (58.8 - 85.8)	55.5 (44.0 - 71.8)	0.003
Missing, n (%)		1 (2.4)	2 (5.9)	
HbA1c (%)		7.5 (6.6 - 8.4)	7.2 (6.6 - 8.0)	0.260
Missing, n (%)			1 (2.4)	

Data are expressed as median (25 - 75%) or number (%). BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate
P-value were derived using Chi-square test or Wilcoxon rank-sum test

Table 3. Comparison of characteristics between normal and low umami taste sensitivity groups

	Umami sensitivity		
	Normal (N - U group) (n=41)	Low (L - U group) (n=34)	P - value
Food intake			
Energy (kcal)	1660 (1495 - 1944)	1714 (1429 - 2233)	0.584
1 group; Milk & dairy products/eggs (g/1000kcal)	103 (63 - 165)	74 (48 - 116)	0.128
2 group; Fish/meats/beans & bean products (g/1000kcal)	117 (64 - 138)	96 (81 - 134)	0.873
3 group; Vegetable/potatoes/fruits (g/1000kcal)	180 (125 - 274)	211 (122 - 285)	0.803
4 group; Grain/sugar/oil/other luxury grocery item (g/1000kcal)	291 (218 - 345)	310 (272 - 399)	0.043
Eating behavior			
Eating frequency of snack (times/day)	1.0 (0.5 - 1.0)	1.0 (1.0 - 2.0)	0.046
Consumption frequency of instant, frozen foods (times/week)	1.0 (0 - 3.0)	1.0 (0 - 2.0)	0.588
Eating frequency supper two hours before bedtime (times/week)	0 (0 - 2.0)	0 (0 - 1.0)	0.433
Eating speed (minutes)	18 (10 - 30)	15 (10 - 30)	0.734
Eating until full (yes), n (%)	17 (41.5)	11 (32.4)	0.417
Umami preference, n (%)	31 (75.6)	17 (50.0)	0.021
Dry mouth, n (%)	26 (65.0)	23 (67.6)	0.810
Missing, n (%)	1 (2.4)		
Periodontal comprehensive examination	**Umami sensitivity**		
	Normal (N - U group) (n=40)	Low (L - U group) (n=29)	P - value
BOP (%)	17.2 (7.2 - 35.7)	11.3 (5.4 - 26.7)	0.269
PCR (%)	37.4 (23.0 - 62.9)	48.2 (32.5 - 66.2)	0.271
PCR>20 %, n (%)	31 (77.5)	25 (86.2)	0.535
PISA (mm^2)	237.0 (77.7 - 516.0)	160.4 (50.9 - 402.5)	0.375
Proportion of teeth/mouth PPD ≥4mm (%)	62.6 (42.1 - 93.7)	51.9 (23.0 - 85.7)	0.254
Proportion of teeth/mouth PPD ≥6mm (%)	8.9 (0 - 36.8)	7.4 (0 - 15.5)	0.508
Prevalence PPD ≥6mm (%), n (%)	27 (67.5)	20 (69.0)	0.897

Data are expressed as median (25 - 75%) or number (%). BOP, Bleeding on probing; PCR, Plaque Control Record; PISA, Periodontal Inflamed Surface Area; PPD, Probing Pocket Depth

P-value were derived using Chi-square test, Fisher's exact test or Wilcoxon rank-sum test

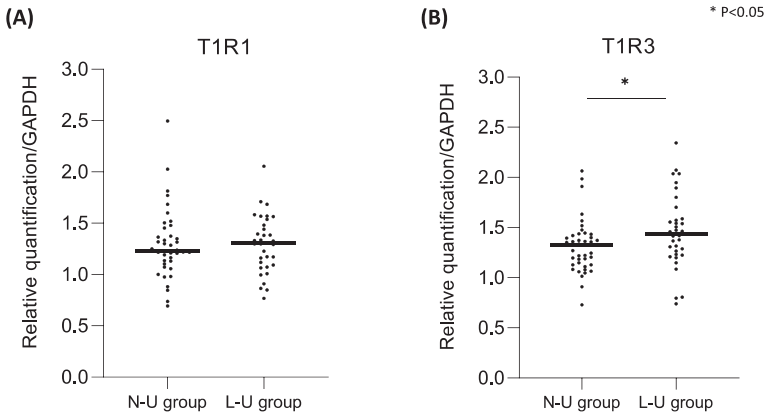

Figure 3. Association between umami taste sensitivity and taste receptor gene expression
Expression levels of (A) T1R1 and (B) T1R3 in the normal umami sensitivity (N-U) and low umami sensitivity (L-U) groups. The relative expression level compared with that of healthy participants was evaluated as 1.
*P < 0.05 Wilcoxon rank-sum test ; N-U group, n = 41 ; L-U group, n = 34

Relationship between umami taste receptor gene expression and oral environment

As shown in Table 3, we did not find any difference in oral environment assessment items between the L-U and N-U groups ; however, when we analyzed the relationship between PCR and T1R3 gene expression, subjects with diabetes with PCR > 20% showed significantly higher T1R3 gene expression than those with PCR ≤ 20% (Figure 4). No association was found between dry mouth, prevalence of severe periodontitis, PISA, and umami taste receptor gene expression (data not shown).

Multivariate analysis for low umami taste sensitivity and high T1R3 gene expression

To determine the relationship between umami sensitivity and T1R3 expression, logistic regression analysis was performed and adjusted for covariates (age and type of diabetes). As shown in Table 4, low eGFR, high intake of grain/sugar/oil/other luxury grocery items, preference for foods with strong umami (dashi), and high T1R3 expression were related to low umami taste sensitivity. Moreover, subjects with PCR > 20% showed high T1R3 gene expression (Table 5).

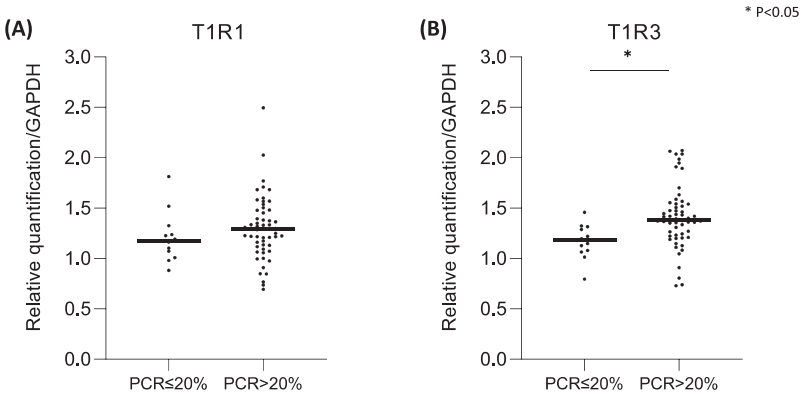

Figure 4. Association between taste receptor gene expression and PCR
Expression levels of (A) T1R1 and (B) T1R3 in PCR ≤ 20% and PCR > 20% groups. The relative expression level compared with that of healthy participants was evaluated as 1.
*P < 0.05 Wilcoxon rank-sum test ; PCR ≤ 20%, n = 13, PCR > 20%, n = 56

Table 4. Multivariate analysis for low umami taste sensitivity

		Model 1		Model 2		Model 3		Model 4	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age		1.02 (0.98 - 1.06)	0.322	1.04 (1.00 - 1.08)	0.082	1.02 (0.98 - 1.06)	0.263	1.05 (1.01 - 1.09)	0.021
Diabetes Type									
	Type 2	Reference		Reference		Reference		Reference	
	Type 1	0.96 (0.23 - 4.02)	0.960	0.47 (0.12 - 1.93)	0.297	0.42 (0.10 - 1.74)	0.229	0.69 (0.17 - 2.69)	0.589
	Others	5.28 (0.53 - 53.07)	0.158	3.49 (0.34 - 36.26)	0.295	5.84 (0.57 - 59.43)	0.136	3.25 (0.32 - 32.96)	0.318
eGFR		0.97 (0.94 - 1.00)	0.033						
Grain/sugar/oil/other luxury grocery item (g/1000kcal)				1.01 (1.00 - 1.01)	0.036				
Umami (dashi) preference (strong preferences)						0.29 (0.10 - 0.87)	0.027		
T1R3 gene expression (high)								3.14 (1.07 - 9.20)	0.037

OR, odds ratio; CI, confidential interval; eGFR, estimated Glomerular Filtration Rate; T1R3, Taste receptor type 1 member 3

Table 5. Multivariate analysis for high T1R3 gene expression

		OR (95% CI)	P-value
Age		0.95 (0.91 - 0.99)	0.025
Diabetes Type			
	Type 2	Reference	
	Type 1	0.64 (0.16 - 2.67)	0.544
	Others	3.43 (0.33 - 36.11)	0.304
PCR (>20 %)		17.75 (2.06 - 153.10)	0.009

OR, odds ratio; CI, confidential interval; PCR, Plaque Control Record

DISCUSSION

We aimed to clarify the relationship between umami taste sensitivity, eating behavior, food intake, and oral environment in subjects with diabetes in present study. As shown described in Figure 5, diabetic pathology, including high blood sugar, is closely related to the oral environment, which is also a critical factor affecting taste sensitivity. In other words, the deterioration of the oral environment in subjects with diabetes due to poor glycemic control and overeating leads to taste disorders, which in turn leads to poor glycemic control and overeating, suggesting a negative association between taste disorders and poor glycemic control. In addition, we examined the involvement of oral hygiene in the mechanism of taste receptor alteration.

Decreased eGFR was associated with low umami taste sensitivity in this study. Taste sense is altered in subjects with CKD, and many of them present with dysgeusia (7). A positive correlation between eGFR and the fungiform papillae area has been previously reported (36). Serum zinc levels decreases, while urinary zinc excretion increases in CKD patients (37). In addition, the quantity of saliva decreases in patients with CKD (38). The mechanism underlying the association between umami taste sensitivity and eGFR in subjects with diabetes is unknown ; however, a close relationship between umami taste and saliva has been suggested (39), and it is possible that decrease in eGFR reduces the area of the tongue papillae where receptors are located, decreasing salivary flow and causing low umami taste sensitivity. Although oral dryness is a serious condition in subjects with diabetes (13), we could not determine the association between oral dryness and umami taste sensitivity in the present study. This might be because the device used in this study is a tool for measuring mucosal humidity retention (24), and salivary flow rate had to be measured directly.

It is interesting that subjects in the L-U group consumed more grain/sugar/oil/other luxury grocery items, that is foods that provided a source of energy, and snacked more frequently in this study. It has been reported that MSG in soups reduces energy intake from high-fat and sweet snacks (40). In addition, MSG stimulates the secretion of the appetite suppressant hormone Glucagon-like peptide-1 (GLP-1) (41). It is possible that low umami taste sensitivity may cause a deficiency in the secretion of appetite-regulating hormones, leading to increased intake of energy-giving foods and increased snacking frequency.

Interestingly, subjects in the N-U group showed a strong preference for umami taste. This is consistent with a report that umami normal tasters preferred foods rich in umami, compared with umami hypo-tasters among Japanese female university students (42). Han *et al*. reported differences in the functional magnetic resonance imaging images for the assessment of MSG stimulation based on umami recognition ability. Umami "high tasters" had a greater activation of the cortical gustatory cortex in response to MSG stimulation, while umami low tasters showed a greater activation of memory-related brain regions, such as the hippocampus and thalamus, suggesting that the perception of umami taste was novel and unusual (43). Our study indicates that individuals with low umami taste sensitivity are not familiar with umami taste.

Regarding the relationship between umami taste sensitivity and taste receptor gene expression in this study, the L-U group showed significantly higher levels of T1R3 expression, compared with the N-U group. Currently, the detailed mechanism underlying T1R3 upregulation in subjects with diabetes with low umami sensitivity is unknown ; however, there are two possible mechanisms. First, the effect of overeating is due to reduced umami taste sensitivity. We previously suggested that overeating in subjects with type 2 diabetes may be responsible for the high levels of taste receptor gene expression (19). No association was found between umami taste sensitivity and energy intake in this study ; however, many of the participants had obesity, and individuals with obesity have been reported to underestimate their dietary intake (44). In addition, many subjects have received nutritional education over time and know the appropriate diet, so it is possible that they answered the appropriate diet for a diabetes, rather than the diet the patient actually ate. The second possibility is that receptor upregulation may occur due to a compensatory function aimed at maintaining normal umami taste sensitivity. The reason why no association was found for the umami taste receptor T1R1 is unknown ; however, T1R3 expression changed during chemoradiotherapy in patients with cancer, whereas T1R1 expression remained unchanged (10). This suggests that T1R3 expression may be particularly sensitive to the external environment.

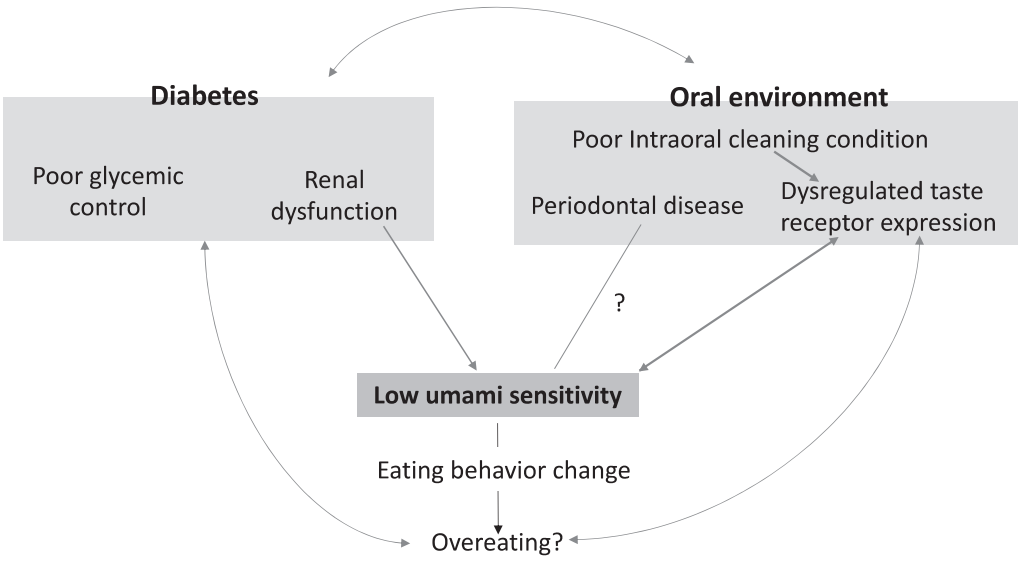

Figure 5. Association of low umami sensitivity with diabetes and the oral environment

Furthermore, subjects with poor oral hygiene and high PCR values showed higher T1R3 gene expression in this study. Poor oral hygiene may inhibit the transmission of taste substances, causing the upregulation of taste receptors to increase the sense of taste. It has also been suggested that plaques on the tongue may inhibit taste substances from accessing taste receptors (45).

We assessed several oral indicators in this study ; however, we did not find any association between periodontal disease and taste receptor gene expression or umami taste sensitivity. Because many subjects were undergoing dental treatment during the survey, the underlying factors affecting the subjects were not completely assessed. Since subjects with diabetes frequently have dental problems, medical doctors usually recommend dental treatment from their initial visit. To understand the relationship between oral status and taste sensation, it is necessary to recruit subjects who are not undergoing dental intervention. This observational study and our previous study show that, normalization of umami taste sensitivity or receptor expression will be helpful in improving dysgeusia in subjects with diabetes. It has been reported that the score indicating low umami taste identification ability significantly increases after training (43). In addition, improved oral hygiene may normalize taste receptor expression and contribute to umami taste sensitivity, and being sensitive to umami taste may normalize contribute to the normalization of receptor expression, dietary therapy, and prevention of complications in subjects with diabetes.

This study has several limitations. First, it was a cross-sectional study ; therefore, the mechanisms underlying reduced umami taste sensitivity and causal relationships could not be clarified. Second, the sample size was small ; therefore, diabetes types or subtypes were not analyzed. A similar trend was observed when only type 2 diabetes was examined, however, it is not clear whether these results are consistent for type 1 diabetes and other types of diabetes. Third, because this study included subjects with diabetes, it was impossible to exclude subjects using drugs that cause dysgeusia as a side effect. Finally, the subjects were at different stages of dental intervention, therefore, despite the investigation of the oral environment and taste and diabetes, it was not possible to determine the effect of the oral environment on taste sensitivity.

In conclusion, our results showed that reduced umami taste sensitivity in subjects with diabetes was associated with low eGFR, food intake, and high umami taste receptor gene expression, and changes in receptor expression were associated with oral hygiene status. Clarification of the mechanisms underlying reduced umami sensitivity and taste receptor changes, focusing on oral hygiene, may expand the possibilities of umami taste sensitivity in diabetic pathology.

DECLARATION OF INTEREST

none.

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Supplemental Table 1. Primer sequence

	Forward primer sequence(5'→3')	Reverse primer sequence(5'→3')
T1R1	CATTCTGGCTGTCTGCAGGTG	CAGGGCCGTGGAGTTGTTTATC
T1R3	TTCCCCCAGTACGTGAAGAC	CAGAGAACGTCTGGTGGTGA
GAPDH	GTGGTCTCCTCTGACTTCAACA	GTTGCTGTAGCCAAATTCGTTGT

Supplemental Table 2. Characteristics of healthy participants

		Total healthy participants (n=22)
Age (years)		57.5 (37.8 - 67.3)
Sex (Male), n (%)		14 (63.6)
BMI (kg/m^2)		23.0 (19.3 - 24.7)
Smoking statue, n (%)		
	Current	2 (9.1)
	Former	7 (31.8)
	Never	13 (59.1)
Systolic blood pressure (mmHg)		125 (112 - 142)
Diastolic blood pressure (mmHg)		78 (65 - 82)
Fasting plasma Glucose (mg/dL)		94 (90 - 101)

Data are expressed as median (25 - 75%) or number (%). BMI, Body Mass Index