ORIGINAL

Taste receptor gene expression is associated with decreased eGFR in patients with diabetes

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Abstract : Dysgeusia is not only associated with zinc deficiency but also with certain drugs or diseases, including diabetes and renal failure. It often lowers the patient's quality of life and hinders access to proper nutrition. The underlying mechanism is unclear and there is a lack of awareness among patients. Here, we focused on lingual taste receptor gene expression in diabetes and elucidated the relationship between taste receptor gene expression and renal function. Forty-seven patients with diabetes and 10 healthy subjects (control group) were enrolled. Lingual foliate papillae were scraped and the derived cDNA was quantified by real-time polymerase chain reaction. Dysgeusia was assessed using SALSAVE®. All statistical analyses were performed using JMP® software 13. The expression of *T1R1* and *T1R2* was significantly upregulated in type 2 diabetes patients as compared with that in healthy subjects ($P<0.01$) but did not change in type 1 diabetes patients. *T1R3* expression positively correlated and *Scnn1* expression negatively correlated with estimated glomerular filtration rate, suggesting that altered taste receptor gene expression could reflect impaired renal function. Thus, alterations in *T1R3* and *Scnn1* expression in diabetes correlated with renal function. Taste receptor gene expression dysregulation could indicate dysgeusia associated with impaired renal function in patients with diabetes. J. Med. Invest. 69 : 120-126, February, 2022

Keywords **:** *Dysgeusia, Diabetes, eGFR, Taste receptor gene*

INTRODUCTION

Dysgeusia causes subjective symptoms such as hypogeusia, ageusia, heterogeusia, and spontaneous abnormal taste perception. Chemicals contributing to taste are detected by receptors expressed on taste cells. Different tastes are recognized following transmission of information to the gustatory area of the cerebrum. Any abnormality in this process results in dysgeusia. Possible causes include side-effects of anticancer drugs (1, 2) and zinc deficiency (3, 4). However, dysgeusia is also common in individuals with systemic diseases such as diabetes and renal failure.

Several studies have indicated that changes in taste perception in patients with diabetes are associated with a decrease in taste susceptibility (5-7). The susceptibility to sweetness is lower in diabetes patients than in healthy individuals but tends to improve with glycemic control (5). The root cause of dysgeusia in diabetes patients is unknown ; however, peripheral neuropathy of the taste nerve and microangiopathy in taste buds may account for diabetic dysgeusia (8). Although numerous reports have revealed the relationship between loss of taste perception and zinc deficiency (9, 10), zinc deficiency alone does not explain dysgeusia in diabetes patients. Several studies have shown that dysgeusia is improved by zinc supplementation (11, 12), whereas some reports have rejected the association of serum zinc levels with taste (13).

Dysgeusia causes anorexia, which in turn reduces the patient's quality of life (QoL) (14). On the other hand, it may also lead to overconsumption of salty or sweetened foods, thereby exacerbating the risks of developing lifestyle-associated diseases. Dietary therapy is very important for patients with diabetes. The maintenance of normal taste function is imperative to ensure proper dietary intake and glycemic control. Patients with diabetes may ingest excessive carbohydrates and sweets owing to a decrease in sweet sensitivity. As a consequence, their blood sugar levels may deteriorate. A decline in the nutritional status owing to improper diet may worsen the prognosis (15, 16). The imbalance in nutrition caused by dysgeusia is largely associated with the incidence and mortality of diabetes and diabetic nephropathy. However, the cause of dysgeusia is unclear, and no effective treatment has been established.

Considering dysgeusia in diabetes patients, we focused on the lingual taste receptor genes in the tongue. The five basic tastes are sour, salty, sweet, umami, and bitter (17) detected by the taste receptors expressed on the taste cells of the lingual taste buds. Sweet, bitter, and umami tastants are G protein-coupled receptors. The sweet taste receptors are T1R2 and T1R3 subunits, the umami receptor comprises T1R1 and T1R3 subunits, and the bitter taste is perceived by > 25 T2R family receptors (18). Skn1a/Pou2f3 is a POU homeodomain protein that is exclusively expressed in sweet, umami, and bitter-tasting cells. Skn1a knockout mice, which exhibit disrupted POU homeodomain protein, cannot detect sweetness, umami, and bitterness, suggesting that Skn1a controls the expression of the corresponding taste receptors (19). The epithelial sodium channel (ENaC) is a Na^+ sensor in taste cells that mediates attraction to sodium salts, and Scnn1a is an ENaC subunit (20). Scnn1a encodes a putative amiloride-sensitive salty taste receptor (21). While sour taste leads to a signal that food is spoiled, several substances such as lactic acid, citric acid, and acetic acid have various health benefits. Candidates for sour taste receptors have been proposed as

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nonselective cation channels formed by polycystic kidney disease 2-like 1 protein (PKD2L1) and polycystic kidney disease 2-like 3 protein (PKD1L3) (22, 23), both of which respond to various types of sour substances (24).

We have previously reported that the taste receptor *T1R3* gene sensing umami and sweet is repressed by chemotherapy (25). This adverse reaction is correlated with an increase in the taste threshold in dysgeusia in patients undergoing chemotherapy for head and neck cancer. We hypothesized that the dysgeusia observed in patients with diabetes is associated with alterations in taste receptor gene expression. Here, we aimed to determine the relationship between taste receptor gene expression and diabetic nephropathy as microvascular complications of diabetes, and to investigate whether taste alteration might be an indirect indicator of microvascular alterations in diabetes. To this end, we analyzed the correlation between the estimated glomerular filtration rate (eGFR) and taste receptor gene expression with gustometry parameters to determine whether worsened renal function correlates with worse gustometry results. Elucidation of the mechanism underlying dysgeusia in diabetes patients may lead to the development of a new therapeutic approach.

MATERIALS AND METHODS

Subjects

Ethical approval for this study was obtained from the ethics committee of Tokushima University, Tokushima, Japan (approval number : 2454). Each participant and/or legal guardian provided written informed consent. We recruited 47 diabetes patients (20 with type 1 diabetes and 27 with type 2 diabetes) who had not undergone hemodialysis therapy and were admitted to Tokushima University Hospital and 10 healthy subjects as a control group (mean age : 55.6 ± 4.8 years ; 5 male and 5 female).

Gene expression analysis

To measure the mRNA expression levels of the taste receptor subunits, the lingual foliate papillae of each patient were scraped from a 2 mL tube with a screw cap. The scrapings were mixed with RNAlater solution (Ambion, Austin, TX, USA) and the RNA was extracted using the RNAqueous phenol-free RNA isolation kit (Ambion, Austin, TX, USA) and amplified with a CellAmp whole transcriptome amplification kit (v. 2 ; TaKaRa Bio Inc., Shiga, Japan) according to the manufacturer's instructions. Total RNA (1 μg) was reverse-transcribed to cDNA in a final volume of 25 μL using a PrimeScript RT reagent kit (TaKaRa Bio Inc., Shiga, Japan). Real-time polymerase chain reaction (RT-PCR) was performed with SYBR green and a StepOnePlus real-time PCR system (Life Technologies, Carlsbad, CA, USA) in a final volume of 10 μL containing 50 ng of the cDNA template and primers. The primers used (human T1R1, T1R2, T1R3, T2R5, Scnn1A, PKD2L1, and Skn-1a) are listed in Table 1. The data were analyzed by relative quantification (RQ), and the results were normalized to glyceraldehyde-3-phosphate dehydrogenase expression.

Taste survey

Taste dysfunction was assessed using the salt-impregnated taste strip SALSAVE® (ADVANTEC, Tokyo, Japan). In addition, patients were interviewed to determine the subjective symptoms related to taste (complexity, loss of taste, and disappearance of taste). The test involved samples with seven separate salt-content levels. The salty taste threshold was determined by touching filter papers to the tongue and indicating the lowest concentration at which saltiness was perceived. Thirty-four of the subjects underwent the SALSAVE test as described in the literature [10]. Where positive subjective symptoms were reported, the period between the onset of the awareness of dysgeusia and the change in taste during treatment was recorded.

Dietary assessment

Patients were asked by a registered dietician about the amount of various food products they consumed on a weekly basis as well as the frequency of such consumption. The semiquantitative food questionnaire administered included 29 food groups and 10 different cooking methods and has been previously validated in Japan. Daily energy and nutrient intake based on the Standard Tables of Food Composition in Japan as well as food group intake were calculated using a nutrient calculation software (Food Frequency Questionnaire ; Kenpaku-sha, Tokyo, Japan).

Statistical analyses

Data are expressed as mean ± standard deviation (SD). To evaluate differences between pairs of groups, Student's *t*-test was performed when the distribution was normal. In cases where the distribution was not normal, Mann–Whitney *U*-test was performed when the variance between groups was equal. Otherwise, Welch's *t*-test was used. To evaluate differences among ≥ 3 groups, a Steel-Dwass test was conducted for non-normal distribution and a Tukey-Kramer test was performed for normal distribution. Correlations were determined using the Pearson and Spearman's correlation tests. Statistical significance was defined as $P < 0.05$. All data were processed using the JMP® software 13 (Tokyo, Japan).

RESULTS

Taste receptor gene expression levels in diabetes patients

The characteristics of the 47 diabetes patients (20 type 1 and 27 type 2) and healthy subjects are shown in Table 2. Type 2 diabetes patients were older, had higher body mass index (BMI),

Table 1. Primer sequences

	Forward primer 5'→3'(sense)	Reverse primer 5'→3'(antisense)
T1R1	CCTCCACATGGTCTCCAGTTCA	TCAAGACAGTCGCTGGAACACAC
T1R2	AATGTCCAGCCGGTGCTCTA	CATCGCTGATGGCGCTGTA
T1R3	CATGCTGGCCTACTTCATCA	TCCCCTGATTTCCTGTGTTC
T2R5	GCTCACATCACTGCGCTGAA	AGGATAGGCTGCCATGAGTGTC
Sccn1A	ATGGAGTGGCCAAAGTCAAC	GAGCAGCATGAGGAACATGA
PKD2L1	ACCTCAGCAGCATCTGGAAC	GGCCAGGAACATGTTCAGGA
GAPDH	CCATGGAGAAGGCTGG	CAAAGTTGTCAGGATGACC

and decreased eGFR than the other patients. There were no significant differences between the groups in terms of hemoglobin A1c (HbA1c) levels and duration of diabetes. Dysgeusia was detected in 35.0% type 1 diabetes patients and 40.7% type 2 diabetes patients. Twenty-six subjects (type 1 diabetes, n = 12 ; type 2 diabetes, n = 14) were surveyed using Food Frequency Questionnaire (FFQg) on their dietary intake frequency. In comparison with type 1 diabetes patients, those with type 2 diabetes had higher total energy and protein intake. On the other hand, the intake levels of nutrients such as fat, carbohydrates, and zinc did not significantly differ between the groups (Table 3). The average salt intake was less than 10 $g \cdot d^{-1}$, but the FFQg analysis revealed that the salt equivalent was > 10 $g \cdot d^{-1}$ in certain cases.

Quantitative analyses of taste receptor gene expression were performed using samples collected from all patients (Fig. 1). The taste receptor gene expression levels are shown relative to those in healthy subjects. The expression of *T1R1* and *T1R2* was significantly higher in type 2 diabetes patients than in healthy subjects ($P < 0.01$) but did not change in type 1 diabetes patients (Fig. 1A-B). The expression of the sweet and umami receptor *T1R3* in diabetes patients was comparable to that in healthy subjects. *T1R3* gene expression did not differ between patients with type 1 and 2 diabetes (Fig. 1C).

The expression of *T2R5*, a bitter taste receptor, was significantly lower in diabetes patients than in healthy subjects ($P < 0.01$, Fig. 1D). *T2R5* gene expression was significantly downregulated in patients with type 2 diabetes than in those with type 1 diabetes ($P < 0.01$). The salty taste receptor *Scnn1A* was expressed at a lower level in most type 1 and type 2 diabetes patients than in healthy subjects, while some patients showed higher *Scnn1A* expression level (Fig. 1E). There was no significant difference in the expression of *Scnn1A* between the type 1 and type 2 diabetes patients. (Fig. 1E). The expression level of the sour taste receptor *PKD2L1* was lower in type 1 diabetes patients than in healthy subjects ($P < 0.05$) but did not change in type 2 diabetes patients. As shown in Fig. 1F, *PKD2L1* expression was higher in patients with type 2 diabetes than in those with type 1 diabetes ($P < 0.01$).

Relationship between reduced renal function and taste receptor gene expression levels

To investigate the relationship between taste receptors and renal function, we analyzed whether the impaired renal function was associated with the diabetes-induced alterations in lingual taste receptor gene expression. As shown in Fig. 2A, a significant positive correlation was detected between *T1R3* gene expression level and eGFR (r = 0.4851 ; $P < 0.01$). On the other hand, a significant negative correlation was observed between the expression level of the salty taste receptor gene *Scnn1A* and eGFR (r = −0.6123 ; $P < 0.01$; Fig. 2B).

Based on the correlation between *T1R3* or *Scnn1* gene expression and eGFR, we next performed a univariate analysis of *T1R3* or *Scnn1A* and each variable (Table 4). In type 1 diabetes, *T1R3* gene expression negatively correlated with HbA1c ($P < 0.031$) and *Scnn1A* expression level negatively correlated with eGFR ($P < 0.025$). In type 2 diabetes, *T1R3* gene expression positively correlated with eGFR ($P < 0.012$) and *Scnn1A* expression level negatively correlated with eGFR ($P < 0.03$). Furthermore, multivariate analyses using a linear model with *T1R3* or *Scnn1A* as a dependent variable in all diabetes patients showed that *T1R3* gene expression positively correlated with eGFR ($P = 0.020$) and *Scnn1A* expression negatively correlated with eGFR ($P < 0.001$) (Table 5).

Table 2. Diabetes patient characteristics

	Healthy subjects	Type 1 diabetes	Type 2 diabetes	*P*
	(n = 10)	(n = 20)	(n = 27)	
Gender (M/F)	5/5	9/11	19/8	
Age (y)	55.6 ± 4.8	49.7 ± 16.4	63.9 ± 12.9	0.0018 **
BMI (kg m^{-2})	21.6 ± 3.5	24.0 ± 5.2	26.5 ± 6.2	0.0369 *
HbA1c (%)	-	7.1 ± 1.1	7.1 ± 0.6	0.8543
eGFR	-	88.5 ± 46.7	53.4 ± 21.0	0.0044 **
Duration of diabetes (y)	-	17.8 ± 11.3	15.7 ± 7.8	0.7838
Dysgeusia (%)	-	35.0	40.7	0.1271

*$P < 0.05$, **$P < 0.01$ type 1 v.s. type 2, Mann–Whitney *U*-test

Table 3. Dietary intake comparison

	Type 1 diabetes	Type 2 diabetes	*P*
	(n = 12)	(n = 14)	
Energy	1786 ± 110	2426 ± 142	0.0021 *
Carbohydrate (g/day)	203.7 ± 26.4	263.5 ± 28.9	0.056
Protein (g/day)	56.0 ± 5.8	76.5 ± 7.2	0.0179 *
Fat (g/day)	50.1 ± 7.8	57.1 ± 9.6	0.065
salt (g/day)	10.1 ± 1.8	11.7 ± 2.4	0.087
zinc (mg/day)	7.8 ± 1.3	9.1 ± 1.8	0.084

*$P < 0.05$, **$P < 0.01$ type 1 v.s. type 2, Student's *t*-test

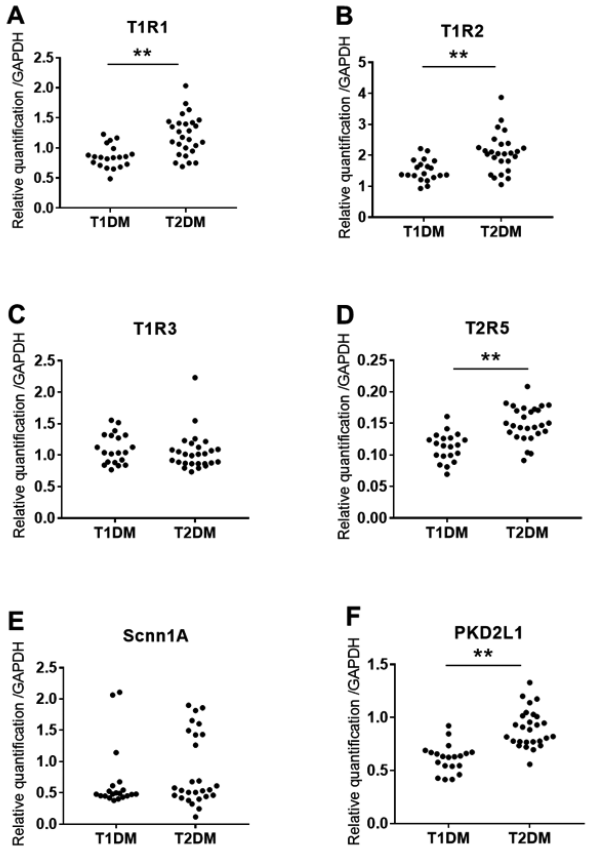

Fig 1. Lingual taste receptor gene expression levels in diabetes patients
Expression levels of lingual (A) *T1R1*, (B) *T1R2*, (C) *T1R3*, (D) *T2R5*, and (E) *Scnn1A* genes in type 1 diabetes (T1DM) and type 2 diabetes (T2DM) patients.
The relative expression level as compared with a healthy subject was taken as 1
$^{**}P < 0.01$, Mann–Whitney *U*-test, T1DM group, n = 20 ; T2DM group, n = 27

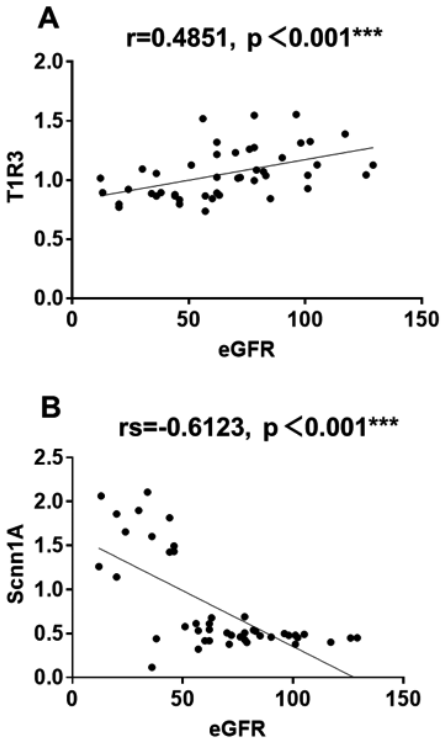

Fig 2. Relationship between decreased kidney function and lingual taste receptor gene expression
Correlation between lingual (A) *T1R3* and (B) *Scnn1A* gene expression levels and eGFR in 45 diabetes patients (type 1 diabetes, n = 19 ; type 2 diabetes, n = 26)
$^{***}P < 0.001$, Spearman correlation test

Table 4. Univariate analysis of T1R3 or Scnn1A and each variabl

		Type1 (n = 20)				Type2 (n = 27)			
		T1R3		Scnn1A		T1R3		Scnn1A	
		ρ or Median (Q1-Q3)	P-value	ρ or Median (Q1-Q3)	P-value	ρ or Median (Q1-Q3)	P-value	ρ or Median (Q1-Q3)	P-value
Age (years)		-0.220	0.350	0.354	0.125	0.181	0.375	-0.408	0.035
eGFR (ml/min)		0.238	0.311	-0.499	0.025	0.487	0.012	-0.419	0.030
Dysgeusia	yes	1.04 (1.03-1.13)	0.562	0.48 (0.45-0.49)	0.958	0.10 (0.87-1.13)	0.244	0.48 (0.35-0.55)	0.471
	no	1.29 (0.86-1.37)		0.48 (0.42-0.54)		1.08 (0.95-1.22)		0.51 (0.41-0.64)	
HbA1c (%)		-0.482	0.031	0.084	0.726	-0.004	0.983	-0.144	0.474

ρ : Spearman's rank correlation coefficient

Table 5. Multiple analysis : linear model with T1R3 or Scnn1A as a dependent variable

	log (T1R3)			log (Scnn1A)		
	B (95% CI)	standard β	P-value	B (95% CI)	standard β	P-value
Diabetic Type (Type1)	0.011 (-0.016,0.039)	0.134	0.407	-0.005 (-0.081,0.072)	-0.017	0.904
Age	0.001 (-0.001,0.002)	0.099	0.541	-0.005 (-0.0100,-0.0004)	-0.304	0.036
log (eGFR)	0.123 (0.021,0.226)	0.377	0.020	-0.679 (-0.963,-0.394)	-0.394	<0.001

95% CI : 95% confidence interval

Relationship between Skn1a transcriptional factor and taste receptor gene expression

We investigated the relationship between the expression of the regulators of taste receptor gene expression associated with dysgeusia and decreased renal function. *Skn1a* is a taste bud-specific gene expressed in sweet, umami, and bitter cells. It controls the differentiation of these cells from their progenitors. There was no significant difference in *Skn1a* expression between healthy subjects and patients with type 1 or type 2 diabetes (data not shown). As shown in Fig. 3A-B, the expression of *Skn1a* was not significantly associated with *T1R3* or *Scnn1A* expression.

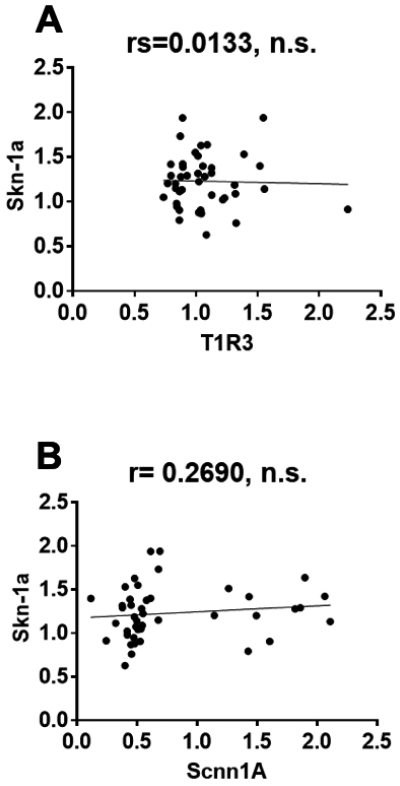

Fig 3. Relationship between the expression of the transcription factor *Skn1a* and lingual taste receptor gene expression levels
Correlation between the expression levels of (A) *T1R3* and (B) *Scnn1A* and *Skn1a* in 43 diabetes patients (type 1 diabetes, n = 19 ; type 2 diabetes, n = 24)
$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, Spearman correlation test

DISCUSSION

In the present study, we analyzed the expression levels of the genes encoding the receptors for all five basic tastes (sweet, bitter, sour, salty, and umami) in diabetes patients and investigated the relationship between taste receptor gene expression and renal function.

In comparison with healthy subjects, type 2 diabetes patients had significantly higher expression levels of *T1R1* and *T1R2*. The expression of the sweet and umami receptor T1R3 was comparable between diabetes patients and healthy subjects. The relationships between dysgeusia and the state of glycemic control and the duration of diabetes have already been reported (5, 26). In the current study, dietary survey results indicated that patients with type 2 diabetes consumed more calories than their actual energy requirements. Highly obese people with a BMI of ~40 $kg \cdot m^{-2}$ routinely ingested approximately 3,000 $kcal \cdot d^{-1}$ despite receiving dietary counselling. In addition to excessive caloric intake, an imbalanced diet is also associated with dysgeusia and may be influenced by the relative expression levels of the tongue taste receptors. We have previously shown that the addition of monosodium glutamate increases taste receptor gene expression (27). Thus, higher *T1R1* and *T1R2* expression levels in patients with type 2 diabetes might be explained by excessive caloric intake and an imbalanced diet.

The expression of *T2R5* and *Scnn1A* was significantly lower in patients with type 1 and type 2 diabetes, and *PKD2L1* expression was lower in type 1 diabetes patients than in healthy subjects. Given that sour signals recognize food is spoiled and that bitter signals recognize non-food substances or dangerous substances, the downregulated expression of these genes may be related to the infectious oral environment in diabetes. Evidence suggests that periodontal infection is associated with an increased risk of diseases such as atherosclerotic vascular diseases and type 2 diabetes (28-31). Further studies are warranted to elucidate the association between the oral environment such as periodontal infection and taste impairment, including taste gene expression.

Skn1a is specifically expressed in sweet, umami, and bitter cells and regulates their differentiation from progenitors. In a previous study, sweet, umami, and bitter cells were found to be entirely absent in *Skn1a* knockout mice, which could not detect the corresponding tastes (19). Our research group also showed that Skn1a is correlated with the human taste receptor gene *T1R3* (27). Skn1a may control the GPCR taste receptors of T1R and T2R families. However, in the present study, we were unable to identify any correlation between Skn1a and T1R3 or Scnn1A. Moreover, there was no difference between type 1 and type 2 diabetes patients in terms of *Skn1a* expression. Although Skn1a is normally expressed in patients with diabetes, it may not efficiently control the differentiation of taste cells. In the present study, we could not determine the regulatory mechanism underlying the association between taste receptor gene expression and dysgeusia and decreased renal function.

However, it is interesting that *Scnn1A* gene expression was lower and correlated with eGFR in all patients with diabetes. Scnn1A is a major subunit of the salty taste receptor ENaC (32). SALSAVE® is generally used to evaluate the salty taste threshold and consists of filter papers impregnated with known stable salt concentrations. Several diabetes patients are known to be unaware of their declining sensitivity to salty taste (6). Although no association was established between salty taste sensitivity and salt intake, routine excessive salt intake may affect tongue taste receptor expression. As salt intake is known to be strongly associated with renal function, excessive salt intake might lead to decreased *Scnn1A* expression and consequently impaired eGFR. Our previous studies on cancer patients revealed that bitter taste receptor gene expression was upregulated in response to anticancer drug administration, and this response was consistent with the spontaneous abnormal taste (25). Thus, the regulation of the expression of taste genes may be reactive or compensatory.

Cancer patients undergoing chemotherapy may, in fact, be aware of and complain about the progressing dysgeusia. Dysgeusia may reduce dietary intake due to anorexia, which in turn diminishes the QoL and results in a poor outcome. In contrast, few patients with diabetes are conscious of any taste abnormalities and maintain their QoL. Dysgeusia in patients without subjective symptoms manifests as a decrease in taste sensation. Although they may be unaware of it, they do not generally tend to become anorexic (6, 7, 14). However, diabetes patients are usually restricted in terms of their diet. In the latter case, salt intake

limitation is indispensable in the maintenance of the disease state and the avoidance of an increase in disease severity (5). A dietary prescription that fails to consider the loss of taste may result in the overconsumption of sugar, salt, and water (5-7). Proper dietary management may be required to prevent dysgeusia.

The present study has a few limitations. First, as this was a small cross-sectional study, we performed multiple analyses in all diabetes patients. Further studies are needed to elucidate the relationship between taste gene expression and renal function in a larger cohort of patients. Second, we did not elucidate the mechanism underlying the regulation of the expression of the taste receptor genes. In this study, we analyzed only the transcription factor Skn1. The mechanism by which T1R3 expression is upregulated in patients with type 2 diabetes is unknown. As the next step, it is necessary to examine the detailed mechanisms by which taste receptor gene expression changes. Third, only *T2R5* expression was examined as a bitter taste receptor gene ; one cannot exclude the contribution of other bitter taste receptor genes to dysgeusia. Thus, further investigation is warranted to establish the exact association between bitter taste gene receptors and dysgeusia.

In the present study, differences in the expression levels of tongue taste receptors among patients with diabetes and diabetic nephropathy were elucidated. In patients with diabetes, the taste receptor *T1R3* and *Scnn1A* gene expression was altered along with their renal functions. Further studies are imperative to determine whether taste receptor gene expression is a new indicator of taste dysgeusia associated with impaired renal function.

CONFLICT OF INTEREST

None

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