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GENETIČKA OSETLJIVOST ČULA UKUSA I BRZINA LUČENJA PLJUVAČKE KOD ORALNE SUBMUKOZNE FIBROZE I DIJABETES MELITUSA TIPA 2: KOMPARATIVNA STUDIJA PRESEKA

GENETIC TASTE SENSITIVITY AND SALIVARY FLOW RATES IN ORAL SUBMUCOUS FIBROSIS AND TYPE 2 DIABETES: A COMPARATIVE CROSS-SECTIONAL STUDY

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Sažetak

Uvod: *Izmenjena percepcija ukusa i smanjena funkcija pljuvačnih žlezda često se javljaju kod sistemskih i oralnih oboljenja kao što su oralna submukozna fibroza (OSMF) i dijabetes melitus tip 2 (engl. type 2 diabetes mellitus – T2DM). Genetska osetljivost na gorko jedinjenje fenil-tiokarbamid (engl. phenylthiocarbamide – PTC), posredovana TAS2R38 receptorima, može pružiti uvid u promene povezane sa bolešću.*
Materijal i metode: *Devedeset ispitanika bilo je ravnomerno podeljeno u tri grupe: OSMF, T2DM i zdrava kontrolna grupa. Osetljivost na ukus testirana je primenom standardizovanih PTC traka koje su bile postavljene na dorzalnu površinu jezika deset sekundi i ocenjena na devetostepenoj skali (1–2 = neosetljivi na ukus, 3–7 = osetljivi, 8–9 = superosetljivi). Nestimulisana pljuvačka se prikupljala pomoću ispljuvavanja koje je trajalo tri minuta, dok se stimulisana pljuvačka dobijala žvakanjem komadića lateksa. Beležen je protok pljuvačke (mL/min). Podaci su analizirani u programu SPSS v22; vrednost p < 0,05 smatrala se statistički značajnom nakon primene odgovarajućih parametarskih i neparametarskih testova.*
Rezultati: *Ispostavilo se da pacijenti sa OSMF-om imaju značajno niže vrednosti PTC-a (1,2 ± 0,5) i manji protok pljuvačke (stimulisana: 2,3 ± 0,2 mL/min, nestimulisana: 0,5 ± 0,1 mL/min) nego ispitanici iz kontrolne grupe. Pacijenti sa T2DM-om imali su smanjeno lučenje pljuvačke (stimulisana: 1,6 ± 0,3 mL/min, nestimulisana: 0,4 ± 0,2 mL/min), ali su zadržali umerenu osetljivost na ukus (5,6 ± 1,3). Pokazalo se da su kod ispitanika iz zdrave kontrolne grupe najviše vrednosti (7,8 ± 0,7) i najveće vrednosti protoka pljuvačke.*
Zaključak: *I OSMF i T2DM povezani su sa poremećenom percepcijom ukusa i funkcijom pljuvačnih žlezda. Testiranje fenil-tiokarbamidom može predstavljati jednostavan dopunski alat u oralnoj dijagnostici. Takođe, uključivanje genotipizacije receptora TAS2R38 moglo bi unaprediti buduća istraživanja.*

Ključne reči: *dijabetes melitus, oralna submukozna fibroza, fenil-tiokarbamid, pljuvačka, percepcija ukusa*

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Abstract

Introduction: *Altered taste perception and reduced salivary gland function are frequently reported in systemic and oral diseases, including oral submucous fibrosis (OSMF) and type 2 diabetes mellitus (T2DM). Genetic sensitivity to the bitter compound phenylthiocarbamide (PTC), mediated by TAS2R38 receptors, may provide insights into disease-related changes.*
Materials and Methods: *Ninety participants were equally divided into three groups (OSMF, T2DM, and healthy controls). Taste sensitivity was tested using standardized PTC strips placed on the dorsal tongue for 10 seconds and scored on a 9-point scale (1–2 = non-tasters, 3–7 = tasters, 8–9 = super-tasters). Unstimulated saliva was collected by the spitting method for three minutes, while stimulated saliva was obtained by chewing latex pieces. Flow rates (mL/min) were recorded. Data were analyzed using SPSS v22, with p < 0.05 considered significant, and appropriate parametric and non-parametric tests.*
Results: *Patients with OSMF showed markedly lower PTC scores (1.2 ± 0.5) and salivary flow (stimulated: 2.3 ± 0.2 mL/min; unstimulated: 0.5 ± 0.1 mL/min) compared with controls. Patients with T2DM had reduced salivary secretion (stimulated: 1.6 ± 0.3 mL/min; unstimulated: 0.4 ± 0.2 mL/min) but retained moderate taste sensitivity (5.6 ± 1.3). Healthy controls demonstrated the highest scores (7.8 ± 0.7) and flow rates.*
Conclusion: *Both OSMF and T2DM are associated with impaired taste perception and salivary function. Phenylthiocarbamide testing may be a simple adjunctive tool in oral diagnostics, while integration of TAS2R38 genotyping could enhance future research.*

Key words: *diabetes mellitus, oral submucous fibrosis, phenylthiocarbamide, saliva, taste perception*

Introduction

Taste receptor cells, located within taste buds of the mouth, throat, larynx, and esophagus, play a crucial role in gustatory perception. In patients with oral submucous fibrosis (OSMF), taste dysfunction may arise from chronic inflammation, reduced blood supply to the tongue, and impaired saliva production, leading to injury of the receptor cells or atrophy of taste buds[1,2,3].

Phenylthiocarbamide (PTC) was first synthesized by Arthur Fox in 1931 and has since been used as a classic genetic marker in population studies[4]. The TAS2R38 gene, discovered in 2003, encodes bitter taste receptors responsible for PTC perception. Two common alleles—one associated with the "taster" phenotype and the other with the "non-taster" phenotype—along with several rare alleles, contribute to inter-individual variability in bitter sensitivity[5,6].

In type 2 diabetes mellitus (T2DM), vascular changes, neuropathy, and impaired immunity can contribute to taste perception disturbances. Reduced salivary secretion, altered composition, and damage to sensory nerve endings in papillae may further exacerbate these changes[7]. Salivary parameters such as flow rate, pH, and protein composition play an important role in gustatory function, as diminished secretion is often associated with impaired taste[8].

Given these associations, the present study aimed to evaluate PTC-mediated genetic taste sensitivity and salivary flow dynamics in OSMF and T2DM patients, and to compare them with healthy controls.

Materials and Methods

This comparative cross-sectional study included 90 participants aged 25–80 years, equally distributed into three groups: patients with oral submucous fibrosis (OSMF), patients with type 2 diabetes mellitus (T2DM), and healthy controls. Participants were selected based on defined eligibility criteria. Individuals with oral submucous fibrosis (OSMF) who did not have any associated systemic illness were included, along with patients diagnosed with type 2 diabetes mellitus who were free from oral lesions and did not report any adverse habits. Healthy participants without any systemic disease or oral pathology were also recruited. Exclusion criteria comprised pregnant individuals, patients with syndromic conditions, and those with systemic, neoplastic, or neurological disorders. Additionally, individuals who were unwilling to participate or those presenting with potential confounding factors such as tobacco or alcohol use, or the intake of medications known to influence taste perception, were excluded from the study.

Taste perception was assessed using PTC paper strips placed on the dorsal tongue for 10 seconds. Participants rated bitterness on a 9-point scale. Scores 1–2 = non-tasters, 3–7 = tasters, 8–9 = super-tasters (Figure 1). In this study, only phenotypic assessment of TAS2R38-mediated bitter taste sensitivity was performed using PTC strips; direct genotyping was not included.

The unstimulated saliva flow rate was detected under controlled temperature and humidity at 11:00, using the spitting method. Unstimulated whole saliva (UWS) was collected for 3 minutes: the undisturbed subject, sitting in a comfortable position, swallowed residual saliva present in the mouth before the beginning of the collection, and then, with the head down and mouth slightly open, saliva was allowed to drip from the lower lip into a pre-weighed, sterile plastic test tube. In the last few seconds of the 3 min, saliva accumulated in the mouth was spat out into the plastic funnel. No other conscious movements of the oral musculature were made during the collection.

Stimulated saliva was obtained with latex pieces (1.0 cm thickness and 12 mm diameter) previously sterilized. Patients expelled saliva into another plastic beaker for 3 minutes (Figure 2).

Data were entered in MS Excel and analyzed using SPSS v22. Descriptive statistics were expressed as mean ± SD or median (IQR), depending on data distribution. Normality was assessed using the Shapiro–Wilk test. ANOVA, Dunnett's, Tukey's, Kruskal–Wallis, and Mann–Whitney U tests were applied where appropriate. A p-value < 0.05 was considered statistically significant.

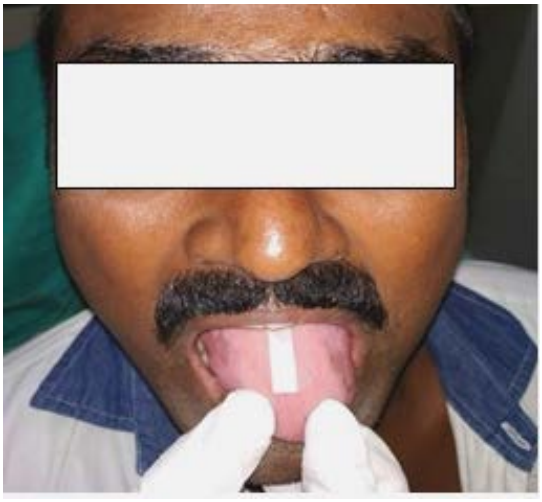

Figure 1. Image showing examination of taste perception using PTC paper strip

Figure 2. Image showing a collection of patient's saliva samples

Results

In this study, we examined 90 respondents aged 25 to 80 years, divided into 3 groups: OSMF, T2DM, and healthy, with each group comprising 30 respondents.

The mean stimulated salivary flow rates were 2.3 ± 0.2 mL/min for OSMF patients, 1.6 ± 0.3 mL/min for T2DM patients, and 3.5 ± 0.4 mL/min for healthy controls (Table 1).

The unstimulated salivary flow rate in OSMF patients was recorded as 0.5 ± 0.1 mL/min, T2DM patients 0.4 ± 0.2 mL/min, and healthy participants 1.1 ± 0.3 mL/min (Table 2).

PTC taste perception and salivary flow rates were significantly different among the groups. When comparing taste perception among three groups using PTC strips, OSMF patients recorded the lowest scores (mean 1.2 ± 0.5), indicating a non-taster phenotype. T2DM patients scored 5.6 ± 1.3, while healthy controls showed the highest sensitivity (7.8 ± 0.7) (Table 3, Figure 3).

Among all evaluated mandibular third molars in Group I, angulation increased in 32.14% of cases, decreased in 46.43%, and remained unchanged in 21.43%. In Group II, angulation increased in 71.43% of third molars, decreased in 17.86%, and remained unchanged in 10.71% of cases (Table 4).

Table 1. Showing stimulated salivary flow rates in all three groups

Variable	Group	**Mean**	**SD**	Median	IQR	Min.	Max.	P-value	O vs. D	O vs. H	D vs. H
Stimulated saliva	OSMF	2.3	0.2	2.3	.3	1.8	2.6	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	T2DM	1.6	0.3	1.6	.5	1.0	2.2				
	Healthy	3.5	0.4	3.5	.6	2.7	4.0				

Table 2. Unstimulated salivary flow rates in all three groups

Variable	Group	Mean	SD	**Median**	**IQR**	Min.	Max.	P-value	O vs. D	O vs. H	D vs. H
Unstimulated saliva	OSMF	0.5	0.1	0.5	.1	.3	.7	**< 0.001**	**0.012**	**< 0.001**	**< 0.001**
	T2DM	0.4	0.2	0.4	.2	.2	1.0				
	Healthy	1.1	0.3	1.2	.5	.7	1.5				

Table 3. Comparison of taste perception among the three groups

Variable	Group	Mean	SD	**Median**	**IQR**	Min.	Max.	P-value	O vs. D	O vs. H	D vs. H
Score	OSMF	1.2	0.5	1.0	0.0	1.0	3.0	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	T2DM	5.6	1.3	6.0	1.3	2.0	7.0				
	Healthy	7.8	0.7	8.0	1.0	6.0	9.0				

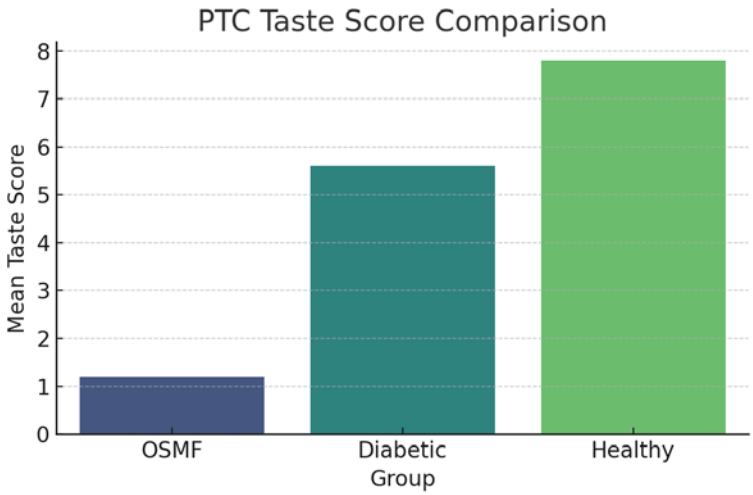

Figure 3. PTC taste score comparison by group

Discussion

This study demonstrates significant impairments in gustatory perception and salivary function among patients with OSMF and T2DM compared with healthy controls. Although both groups exhibited reduced salivary flow, the pattern of taste dysfunction differed, reflecting the combined effects of genetic predisposition, salivary physiology, and disease-specific pathology.

Taste Physiology and Salivary Contribution

Taste buds, located primarily on the tongue papillae, contain receptor cells that transmit chemical signals via cranial nerves VII, IX, and X[6,9]. Saliva is essential for dissolving tastants, transporting them to receptor sites, and maintaining taste bud function. Reduced secretion impairs this process, causing receptor damage, atrophy of taste buds, and ultimately diminished sensitivity[10,11]. In this study, both OSMF and T2DM patients showed significantly reduced stimulated and unstimulated salivary flow compared with controls, consistent with earlier findings by Kadher et al., who reported markedly reduced secretion in OSMF patients[12]. In diabetes, hyposalivation may be aggravated by hyperglycemia, neuropathy, and microvascular dysfunction, with severity correlating with glycemic control[7,13].

TAS2R38 Genetic Variation and Phenotypic Testing

Phenylthiocarbamide strips were used in this study as a phenotypic tool to assess genetic taste sensitivity. Phenylthiocarbamide, also known as phenylthiourea, belongs to the thiourea class of organosulfur compounds and is notable for its highly variable taste perception—ranging from very bitter to tasteless—depending on individual genetic makeup[14]. This inter-individual variability is a classic Mendelian trait, primarily mediated by polymorphisms in the TAS2R38 gene[4,14].

The TAS2R38 gene, located on chromosome 7q, encodes the T2R38 bitter receptor protein. PTC binds to the apical microvilli of taste receptors encoded by this gene, triggering G-protein–coupled signaling via gustducin and initiating a cascade that produces the sensation of bitterness[15]. Three nonsynonymous polymorphisms (A49P, V262A, I296V) give rise to two predominant haplotypes: PAV, associated with the taster phenotype, and AVI, associated with the non-taster phenotype. Individuals homozygous for PAV/PAV perceive strong bitterness, AVI/AVI homozygotes are insensitive, and heterozygotes (PAV/AVI) exhibit intermediate sensitivity. Importantly, TAS2R38 is one of the few taste receptor genes with a consistent genotype–phenotype correlation for both PTC and PROP (6-n-propylthiouracil) sensitivity[16,17].

In this study, phenotypic testing was performed using PTC strips. Although this approach is validated and widely used to evaluate genetic taste variation[10], it cannot fully differentiate between true genetic non-tasters and individuals whose reduced sensitivity results from disease-related local changes. Nevertheless, prior research has demonstrated strong concordance between PTC phenotype and TAS2R38 genotype18, supporting the clinical relevance of phenotypic testing as a practical and accessible method in oral diagnostic research.

Impact of OSMF on Taste Perception

OSMF is a chronic, progressive, and irreversible condition characterized by epithelial atrophy and submucosal fibrosis. Chronic areca nut chewing contributes to local cytotoxicity through the release of alkaloids, flavonoids, polyphenols, and nitrosamines, which undergo nitrosation and generate oxidative stress[10,19]. These biochemical alterations, combined with fibrosis, compromise salivary gland function and directly impair taste buds, resulting in diminished gustatory sensitivity. In this study, OSMF patients frequently exhibited a non-taster phenotype, aligning with previous findings of altered perception across sweet, sour, salty, and bitter modalities, with advanced stages particularly affecting salt sensitivity[2,11,20,21].

Impact of T2DM on Taste Perception

In contrast, T2DM patients retained partial PTC sensitivity despite reduced salivary flow. This suggests that TAS2R38 receptor function may remain relatively intact, with taste deficits arising instead from neuropathy, vascular compromise, and salivary gland dysfunction[7,13,22]. These findings highlight distinct pathogenic mechanisms in OSMF and diabetes.

Confounding Factors

Taste and salivary function can be influenced by age, sex, medications, nutrition, and lifestyle habits[8]. Although the present study minimized comorbidities through exclusion criteria, residual confounding cannot be entirely excluded. Larger studies with stratification and multivariate analysis are needed to address these influences more robustly.

Relationship between Salivary Flow and Taste

This study confirmed that both OSMF and T2DM groups had significantly lower salivary flow than controls. Patients with the lowest salivary secretion also tended to exhibit the poorest PTC sensitivity, supporting the hypothesis that saliva plays a critical role in maintaining taste function[16]. However, the persistence of moderate PTC sensitivity in T2DM patients despite hyposalivation suggests that factors beyond saliva, such as neuropathy, may modulate taste in T2DM[6].

Clinical Implications

Altered taste perception and xerostomia can significantly affect dietary choices, reduce nutritional intake, and impair quality of life[23]. For dental practitioners, recognizing these deficits can aid in counseling patients, guiding dietary modifications, and preventing malnutrition-related complications. Early detection of taste and salivary changes may also serve as a marker for disease progression or severity in OSMF and T2DM.

Certain limitations should be considered when interpreting these findings. The absence of TAS2R38 genotyping limits the ability to distinguish between genetic influences and disease-related changes in taste perception. The cross-sectional nature of the study also restricts any inference of causal relationships. In addition, the relatively small sample size may affect the generalizability of the results, and despite careful selection criteria, the possibility of residual confounding cannot be completely excluded.

Conclusion

This study highlights that patients with OSMF show marked impairment in bitter taste perception, largely presenting as non-tasters, while those with T2DM retain partial sensitivity despite reduced salivary flow. These findings suggest that local pathological changes such as fibrosis and salivary alteration, play a dominant role in OSMF, whereas neuropathic and metabolic factors contribute to diabetes. Although only phenotypic testing was performed, the results underscore the clinical relevance of taste assessment as an early indicator of disease impact. Future studies integrating TAS2R38 genotyping and salivary profiling are essential to better differentiate genetic predisposition from disease-related impairments and to improve nutritional and quality-of-life outcomes in these patients.

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