Impaired taste sensation in type 2 diabetic patients without chronic complications: a case-control study

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Impaired taste sensation in type 2 diabetic patients without chronic complications. A case-control study.

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Abstract

Purpose*:* Few and contradictory data suggest changes in taste perception in type 2 diabetes (T2DM), potentially altering food choices. We therefore analyzed taste recognition thresholds in T2DM patients, with good metabolic control and free of conditions potentially impacting on taste, compared with age-, body mass index- and sex-matched normoglycemic controls.

Methods*:* An ascending-concentration method was used, employing sucrose (sweet), sodium chloride (salty), citric acid (sour) and quinine hydrochloride (bitter), diluted in increasing concentration solutions. The recognition threshold was the lowest concentration of correct taste identification.

Results: The recognition thresholds for the 4 tastes were higher in T2DM patients. In a multiple regression model, T2DM [β=0.95; 95%CI 0.32-1.58; p=0.004 (salty); β=0.61; 0.19-1.03; p=0.006 (sweet); β=0.78; 0.15-1.40; p=0.016 (sour); β=0.74; 0.22-1.25; p=0.006 (bitter)] and waist circumference [β=0.05; 0.01-0.08; p=0.012 (salty); β=0.03; 0.01-0.05; p=0.020 (sweet); β=0.04; 0.01-0.08; p=0.020 (sour); β=0.04; 0.01-0.07; p=0.007 (bitter)] were associated with the recognition thresholds. Age was associated with salty (β=0.06; 0.01-0.12; p=0.027), and BMI with sweet thresholds (β=0.06; 0.01-0.11; p=0.019).

Conclusions*:* Taste recognition thresholds were higher in uncomplicated T2DM, and central obesity was significantly associated with this impairment. Hypogeusia may be an early sign of diabetic neuropathy and be implicated in the poor compliance of these patients to dietary recommendations.

Key words: hypogeusia, obesity, taste thresholds, type 2 diabetes mellitus, waist circumference.

Introduction

Compliance to dietary recommendations is usually poor in patients with type 2 diabetes (T2DM) [1]. The change in sweet taste perception might alter food preferences and may be one of the causes of such low adherence, [2]. In particular, sugar taste perception has been reported to be reduced in both type 1 and T2DM patients [3,4,5]. This impairment could increase the preference for sweet foods [6] and it is associated with a worse metabolic control [7], ameliorating after glucose improvement [4].

The salty threshold seemed to be increased in newly diagnosed T2DM patients too [4], above all in those with uncontrolled hyperglycemia [7]. Furthermore, a correlation between a raised salty threshold, dietary sodium intake and hypertension has been found [8-9], thus suggesting a possible connection between taste alterations and cardiovascular risk in T2DM patients. Data about the perception of sour or bitter taste in these patients are scarce and often contradictory [3,7,10].

The taste alterations of T2DM patients have been associated with the reduction of salivary flow, dry mucosa, coated tongue, zinc deficiency, reduced production of carbonic anhydrase VI, a salivary protein, which is reduced in individuals with hypogeusia [11]. Other potential explanations have been proposed, such as: microangiopathy involving the taste bud with alterations of the fungiform papillae [12], reduced secretion of glucagon-like peptide-1 (GLP-1) with impaired modulation of the sweet taste [13], disordered control of intestinal sweet taste receptors [14], the activation of taste cells inhibiting the gustatory response to sweet compounds induced by the hyperleptinemia secondary to insulin resistance [2]. Finally, neuropathy of the taste sensing nerves can affect taste thresholds, and a relationship between peripheral neuropathy, autonomic neuropathy and hypogeusia in patients with longer diabetes duration has been reported [3,15]. Indeed, hypogeusia has been described also in early diabetes and in patients without peripheral neuropathy [4-5,7].

The reasons for the controversial reports might be due to the heterogeneity of the analyzed individuals, the different techniques used to measure taste thresholds, and the concomitant

conditions which may impact on taste perception, such as older age [16], smoking [3-4], presence of neuropathy [3-4], use of hypoglycemic and/or other drugs [4,7], uncontrolled diabetes [3,5,7].

We aimed therefore to analyze the taste recognition thresholds in a group of adult DMT2 patients with controlled diabetes, free of chronic complications, and other conditions potentially impacting on taste perception, compared with age-, body mass index (BMI)- and sex-matched normoglycemic controls.

Methods

Subjects

This case-control observational study was conducted to compare the recognition threshold for salty, sweet, sour, and bitter tastes in T2DM patients and normoglycemic controls through a functional test.

From March 2016 to June 2016, all the consecutive T2DM patients attending the Diabetic Unit of the "Città della Salute e della Scienza" hospital, were evaluated for enrollment. Inclusion criteria were: age between 18 and 65 years and glycated hemoglobin (HbA1c) < 8%. Exclusion criteria were: presence of any clinic or instrumental sign of neuropathy, retinopathy, nephropathy, active smoking, assumption of any drug affecting the taste perception (e.g., antianxiety agents, anti-bacterials and anti-fungals, antidepressants, antiepileptic drugs, antihypertensive and cardiac drugs, antihistamines and decongestants, anti-inflammatory agents, anti-migraine agents, anti-parkinsonian drugs, antipsychotics, antiviral agents, bronchodilators, hypnotics, pancreatic enzyme preparations, smoking cessation aids, thyroid drugs) [17], presence of comorbidity impacting on taste (renal or liver diseases, actual cancer or previous history of cancer, previous head and neck radiation treatment, hypothyroidism, acute or chronic neurodegenerative diseases, major depressive disorders, acute infections in the previous 2 weeks, respiratory diseases, Sjogren disease, oral or dental diseases, anosmia), and denture carriers.

The controls were healthy, non-diabetic volunteers, i.e. asymptomatic individuals, not taking hypoglycemic drugs or any other drug, with normal fasting glucose values. They were matched for sex, age and body mass index to the T2DM patients.

Ethical issues

The study protocol was approved by the local Ethical Committee, the procedures were in compliance with the Helsinki Declaration principles. All the participants provided written informed consent to participate in the study.

Taste perception tests

A validated forced-choice ascending-series method was used to measure the taste perception thresholds [18-19]. Tastants and the concentrations used to test the perception thresholds were derived from previous studies [5,20]. In particular, the following substances were employed: sucrose for the sweet taste [5,20], sodium chloride for salty [20], citric acid for sour [20], and quinine hydrochloride for bitter taste [20]. Tastants were diluted in deionized water in a series of ten progressively increasing concentration solutions. Each dilution step differed from the previous one by a dilution factor of 2, and the concentrations ranges were 1.25×10^{-3} to 6.4×10^{-1} mol/L for sucrose [5,20], 1.25×10^{-3} to 6.4×10^{-1} mol/L for sodium chloride [20], 4.88×10^{-5} to 2.5×10^{-2} mol/L for citric acid [20], and 3.11×10^{-7} to 1.6×10^{-4} mol/L for quinine hydrochloride [20]. A number was given to each dilution, with 1 corresponding to the highest dilution (the best recognition threshold) and 10 to the lowest dilution (the worst recognition threshold).

During each step, three 30 mL plastic glasses were presented to participants in a random order; one of these contained 15 mL of a stimuli solution, the other two contained 15 mL of deionized water. Participants were asked to identify which of the three glasses contained the solution, and then to describe the solution (sweet, sour, etc). The recognition threshold was defined as the lowest concentration at which participants correctly identify and describe the taste. Subjects took the

solution into the mouth and then were required to expectorate it and wash their mouth with deionized water to avoid carry-over effects.

The order of taste presentation was randomized. During each step, tastants were presented at increasing concentrations.

Measurements

Participants performed the taste tests in a dedicated room, free from noise and smells, between 9:00 and 11:00, after 8-10-h fasting and after avoiding spicy foods for 24-h before testing.

A 24-hour dietary recall interview was performed by a skilled dietitian.

Weight, height, and waist circumference were measured in all the participants by trained researchers. Body weight was determined to the nearest 0.1 kg by a mechanical column scale (SECA model 711, Hamburg, Germany), height to the nearest 0.1 cm by a stadiometer (SECA 220 measuring rod, Hamburg, Germany) with the participants wearing light clothes and no shoes. Waist circumference was measured to the nearest 0.1 cm by a tape.

Before the test, blood glucose values were measured by a glucometer (Roche Diagnostic Accu-Chek Inform II, Basilea, Switzerland).

Blinding

The researchers who performed the experiment were blinded to the content of the glasses. The different tastes were presented to the subjects in a randomized order.

Statistical analyses

A total of 25 T2DM and 25 non-diabetic subjects were needed to obtain a power of 90% with a two-tailed α-value=0.05, based on published results [5].

Data are presented as mean and SD. T-Student or chi-square test, as appropriate, were used to analyze variable differences between T2DM patients and controls. Pearson's correlations coefficients

between taste recognition thresholds and anthropometric, biochemical, and nutritional characteristics were calculated.

A multiple regression model was used to evaluate the association among the taste perception thresholds and clinical characteristics of the whole sample, after adjustments for age, gender, BMI, waist circumference and presence of T2DM. The goodness of fit of the model was calculated by R^2 statistics.

Results

The characteristics of the T2DM patients and controls are reported in **Table 1**. The two groups were similar for age, gender distribution, weight, BMI, waist circumference, but differed for fasting glucose values, as expected. No diabetic patient had impaired kidney function or a history of cardiovascular disease and zinc deficiency, as assessed by the clinical records filled out by the diabetologists.

All T2DM patients received a diet by a trained dietitian; their reported intake of fiber was significantly higher than that of controls. Other nutritional values did not differ significantly.

The recognition thresholds for all 4 analyzed tastes were higher in T2DM patients (**Table 2**).

The Pearson correlations between each taste recognition threshold and clinical and anthropometric variables are described in **Table 3**. The salty perception threshold was significantly associated with age and waist circumference in the cases; the sweet threshold was correlated with BMI and waist (both cases and controls) and HbA1c (cases); the bitter threshold was inversely associated with age and directly with waist circumference in cases only.

In a multiple regression model, both the presence of T2DM and waist circumference values were significantly associated with all the taste recognition thresholds (**Table 4**). Age was associated with the salty threshold, and BMI with the sweet threshold. In the same model, HbA1c levels were directly associated with the salty (β=0.38; 95%CI 0.05-0.71; p=0.035) and sweet (β=0.37; 95%CI 0.14-0.60; p=0.005) thresholds in the group of T2DM patients. No significant associations were found with fasting glucose values.

R^2 indicated acceptable goodness of fit for the sour model, and good values for the other taste models.

Intriguingly, the percentage of simple sugars was significantly associated with the sweet recognition threshold both in T2DM patients (r=0.44; p=0.026) and in controls (r=0.42; p=0.036), while sodium intake was associated with the salty recognition threshold (r=0.52, p=0.007) in T2DM only.

Discussion

The recognition thresholds for salty, sweet, sour and bitter tastes were higher in patients with uncomplicated T2DM than in the normoglycemic age-, BMI- and sex-matched controls. Greater waist circumference values were associated with a worse perception for all the tastes, while an increased BMI was associated with a reduced sensitivity for sweet tastes.

Many pathophysiological mechanisms have been proposed to explain the hypogeusia of patients with diabetes mellitus. Oral complications are very common in T2DM and include periodontal diseases, burning mouth syndrome, mouth dryness, and trigeminal pain [21]. Xerostomia has been reported in more than 50% of patients and it correlates with oral mucosal disorders [22]. A low salivary flow is responsible for taste alterations, due to the reduction of gustin and carbonic anhydrase VI, a zinc-dependent metalloprotein acting as salivary grow factor and allowing the maturation of taste papillae and the homeostasis and integrity maintenance of the gustatory receptors [23]. Increased density of saliva, as well as the presence of oral mycosis and tongue coating can also hamper the transport of taste chemicals to the taste buds [24].

The diabetic hypogeusia has been associated with microangiopathy and impaired blood vessel density and morphology at the tip of the tongue [12]. Furthermore, olfactory deficits, negatively impacting on taste sensitivity, are frequently found in diabetes [25]. Finally, the peripheral neuropathy with involvement of the lingual nerve has been proposed as a cause of gustatory alterations in these patients [3-4]. The taste thresholds were found to increase with increasing

severity of diabetic neuropathy, i.e. from neuropathy-free to non-autonomic neuropathy to autonomic neuropathy [4,15]. However, available data on this topic were discordant, since taste impairment has been found in patient without neuropathy, and gustatory defect improved after the achievement of a good glycemic control, independently of neuropathic complications [4,7].

We herein have shown that in T2DM patients with good glycemic control, without neuropathy, the recognition thresholds for the four main tastes were increased with respects to controls. In diabetes, as in other degenerative diseases [26], hypogeusia may precede the onset of chronic complications [27], thus potentially representing by itself an early complication of T2DM. A strong correlation between hypogeusia worsening and neuropathy progression was found in T2DM patients, since the initial taste impairment predicted the presence of diabetic complications after 5 years in almost 90% of cases [28]. Furthermore, the functional changes in glucose receptor proteins (TAS1R2/TAS1R3 receptor, α-gustducin, SGLT-1, GLUT-2), leading to T2DM, could impact early on taste sensitivity, by increasing the sweet taste threshold [14,29-30].

The diagnosis of taste impairments by functional tests or electric gustometry may have therefore a role in the early detection of patients at risk of developing other degenerative complications [28].

We have found a direct association between waist circumference and increased recognition thresholds for the four tastes. Accordingly, an increase in visceral fat was found to be associated with the decrease in the gustative and olfactory function in adult women across different BMI categories [31]. In obese mice, a prolonged high fat diet reduces the peripheral taste signals, influencing food preferences [32].

Taste alterations have been demonstrated in 25% of obese subjects [33]; a lower sensitivity to sweet could also lead to a greater quantity of energy-dense food consumption with weight gain [34]. Indeed, weight loss resets the taste thresholds, especially for sweet perception [35]. The interaction between the circulating levels of leptin, the function of the taste cells [36] and the dopaminergic

system, modulating food gratification [37], might be responsible for hypogeusia in obesity. Furthermore, taste sensitivity is modulated by GLP-1 through a paracrine signaling between the taste buds and the intragemmal afferent nerve fibers [38] and oral health is worse in the presence of obesity, thus predisposing to hypogeusia [39].

The association between body weight and impaired taste perception has already been described in diabetic patients [16], while in normal-weight T1DM patients, no correlations have been reported [3].

Individual tastes

The impairment of sweet sensitivity in diabetic patients has been demonstrated for the first time nearly 30 years ago [3]. The sensory deficit improves after hyperglycemia correction and is more severe in patients with overt peripheral sensory neuropathy and longer disease duration [4]. Individuals with pre-diabetes demonstrate higher, but not significantly different detection and recognition thresholds than normoglycemic controls [5].

Sweet sensitivity correlates with HbA1c values, in accordance with our results [7]. We did not show a correlation between fasting glucose values and the taste thresholds in the group of T2DM patients, in agreement to previous results [3], whereas correlations were found in studies including patients with poor glycemic control [7].

Data relative to the perception of other tastes in T2DM are contradictory. A higher threshold for salty taste has been described by some [4,7,10,30], but not all the authors [3]. An altered bitter taste perception was reported in older studies [3,10], but not further confirmed [4,7,30]. Similarly, an impaired sour perception has been shown by some authors [4,10], but not by others [3,7]. These highly controversial results might be due to the great heterogeneity among studies in the enrolled patients, with differences in glycemic control, presence of chronic complications, use of drugs, and other possible confounders.

Indeed, in our highly selected T2DM patients, we could highlight increased recognition thresholds for all the tastes, showing that a multidimensional hypogeusia is present at an early stage of the disease.

Clinical implications

The taste threshold impairment might determine the seek of foods containing more flavors, such as salty and sweet foods [5,40-41], thus explaining at least in part the poor compliance to dietary recommendations of many T2DM patients [1]. Furthermore, foods stimulate the whole gustatory system simultaneously and much more than individual taste diluted in water [42]. We have found a direct correlation between intakes of simple sugars and sodium and respectively the sweet and salty recognition thresholds in these patients. Accordingly, a recent study has shown that total sugar intake was significantly higher in patients with diabetes or prediabetes and sweet taste disorder [43]. An increased consumption of sugars has been reported to be associated with metabolic impairments hypertension, cardiovascular diseases and mortality [44-46]. Most importantly, the impaired sweet perception was associated with diabetic chronic complications, such as retinopathy and nephropathy, and with a more than 2-fold risk of ischemic heart disease [43]. Cells with taste receptors are also present in the intestine and their dysregulation has been reported to be associated with increased glucose absorption and post-prandial hyperglycemia in T2DM patients [47]. Therefore, an enhanced sugar intake and absorption has been hypothesized as possible causes of increased glucose values and fluctuations leading to chronic and vascular complications in patients with abnormal glucose tolerance [43].

Furthermore, our results pointed out a direct association between age and salty perception, even if older patients were not included. Aging is responsible for changes in taste perception and smell [42,48-49], and impairments in the perception thresholds of salty sour and bitter tastes, but not sweet, have been found [42,50-52]. The chronic sub-clinic pro-inflammatory state associated with T2DM may accelerate aging [53]. Therefore, our adult T2DM patients showed a taste pattern similar

to that of older but healthy individuals, suggesting that diabetes accelerates the aging of all body functions, including taste sensitivity.

This knowledge can be used to advise T2DM patient to use ingredients that enhance the flavors: herbs, spices, potassium chloride, non-nutritive sweeteners and sweetener enhancers, in order to limit sodium and sugar intake [1,54-55].

Limitation

The limitations of the present study were the low number of individuals evaluated, its cross-sectional design, the lack of the measurements of HbA1c values in the normoglycemic controls. We failed to find significant differences in the dietary habits of T2DM patients when compared to healthy controls, with the exception of a significantly lower fiber intake in the controls, despite the higher recognition thresholds of the former individuals. Indeed, all our T2DM patients have received a diet by a trained dietician, and the reported intakes of simple sugars and sodium were quite different from the recommended portions (<10% simple sugars; <2.4g sodium). Therefore, we could hypothesize that the difficulty in following the diet, documented by the similarity of our patients' intakes with those of non-diabetic individuals, similarly to what reported in other cohorts [56], might depend, at least in part, on their hypogeusia.

The strengths were the measurement of anthropometric and dietetic variables by trained researchers, and the very strict exclusion criteria, allowing us to exclude confounding factors impacting on taste perception.

Conclusions

Taste recognition thresholds were higher in uncomplicated T2DM, and central obesity was significantly associated with this impairment. Further researches in larger samples are needed to evaluate whether hypogeusia may be an explanation for the low compliance to dietary recommendations of T2DM patients.

Table 1. Characteristics and nutritional intakes of cases and controls

	T2DM patients	Controls	P
Number	25	25	
Age (years)	56.8±6.7	56.2±4.9	0.68
Males (%)	72	72	1.00
Weight (kg)	82.4±15.7	80.6±11.2	0.64
BMI (kg/m^2)	28.6±5.3	28.3±4.4	0.87
Waist circumference (cm)	100.7±10.3	101.6±10.6	0.77
Fasting glucose (mg/dl)	121.4±21.0	95.6±9.3	<0.001
Glycated hemoglobin (%)	6.7±1.4	-	-
Dietary intakes:			
Energy (total Kcal)	1614.6±539.2	1717.5±537.1	0.50
CHO (% kcal)	52.3±8.4	48.3±8.2	0.09
Simple sugars (% kcal)	13.1±3.8	13.4±5.4	0.79
Fat (% kcal)	31.6±7.5	33.6±7.8	0.35
Proteins (% kcal)	16.1±4.0	17.6±4.9	0.23
Fiber (g/day)	28.4±4.4	23.3±5.4	<0.001
Sodium (mg/day)	3690.7±384.3	3927.4±583.5	0.10

CHO=carbohydrates

Table 2. Recognition thresholds of T2DM patients and controls

	T2DM patients	Controls	P
Salty (NaCl)	6.0±1.2	5.1±1.3	0.008
Sweet (sucrose)	5.3±0.9	4.7±0.8	0.019
Sour (citric acid)	5.3±1.3	4.6±1.0	0.029
Bitter (quinine HCl)	3.5±1.0	2.8±1.0	0.020

Table 3. Correlations between taste recognition thresholds and anthropometric, biochemical, and nutritional characteristics in T2DM patients and controls

	T2DM patients				Controls			
	Salty	Sweet	Sour	Bitter	Salty	Sweet	Sour	Bitter
Age	**r=0.40** p=0.049	r=-0.14	r=-0.12	**r=-0.51** p=0.009	r=0.04	r=-0.05	r=0.09	r=0.14
Males	r=0.18	r=0.31	r=0.23	r=0.12	r=0.18	r=-0.11	r=0.08	r=0.24
BMI	r=0.04	**r=0.42** p=0.038	r=-0.27	r=0.11	r=0.29	**r=0.53** p=0.007	r=0.15	r=0.29
Waist circumference	**r=0.52** p=0.007	**r=0.48** p=0.014	r=-0.27	**r=0.52** p=0.007	r=0.33	**r=0.51** p=0.009	r=0.29	r=0.39
Fasting glucose	r=0.12	r=0.15	r=0.25	r=-0.06	r=0.18	r=0.17	r=-0.19	r=0.04
Glycated hemoglobin	r=0.33	**r=0.67** p<0.001	r=0.06	r=0.12	-	-	-	-

Table 4. Association among the taste recognition thresholds and clinical characteristics of the whole sample in a multiple regression analysis

	β	95% CI		P
Salty perception threshold				
Age (years)	0.063	0.008	0.119	**0.027**
Male gender	0.493	-1.222	0.237	0.181
BMI (kg/m^2)	0.015	-0.060	0.090	0.686
Waist circumference (cm)	0.045	0.010	0.080	**0.012**
Presence of T2DM	0.953	0.322	1.585	**0.004**
Sweet perception threshold				
Age (years)	-0.002	-0.040	0.035	0.909
Male gender	0.253	-0.742	0.237	0.304
BMI (kg/m^2)	0.061	0.011	0.111	**0.019**
Waist circumference (cm)	0.028	0.005	0.051	**0.020**
Presence of T2DM	0.612	0.188	1.035	**0.006**
Sour perception threshold				
Age (years)	-0.009	-0.064	0.047	0.758
Male gender	0.021	-0.747	0.705	0.954
BMI (kg/m^2)	-0.064	-0.138	0.011	0.092
Waist circumference (cm)	0.041	0.007	0.076	**0.020**
Presence of T2DM	0.777	0.148	1.405	**0.016**
Bitter perception threshold				
Age (years)	-0.031	-0.077	0.015	0.178
Male gender	0.248	-0.846	0.349	0.407
BMI (kg/m^2)	0.003	-0.058	0.064	0.925
Waist circumference (cm)	0.040	0.012	0.068	**0.007**
Presence of T2DM	0.736	0.218	1.253	**0.006**

Ethical approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1) Rivellese AA, Boemi M, Cavalot F, Costagliola L, De Feo P, Miccoli R, Patti L, Trovati M, Vaccaro O, Zavaroni I (2007) Dietary habits in type II diabetes mellitus: how is adherence to dietary recommendations? Eur J Clin Nutr 62:660-664

2) Loper HB, La Sala M, Dotson C, Steinle N (2015) Taste perception, associated hormonal modulation, and nutrient intake. Nutr Rev:83-91

3) Le Floch JP, Le Lievre G, Sadoun J, Perlemuter L, Peynegre R, Hazard J (1989) Taste impairment and related factors in type I diabetes mellitus. Diabetes Care 12:173-178

4) Perros P, Counsell C, Mac Farlane TW, Frier BM (1996) Altered taste sensation in newly-diagnosed NIDDM. Diabetes Care 19:768-770

5) Wasalathanthri S, Hettiarachchi P, Prathapan S (2014) Sweet taste sensitivity in pre-diabetics, diabetics and normoglycemic controls: a comparative cross-sectional study. BMC Endocr Disord 14:67. doi:10.1186/1472-6823-14-67

6) Noel CA, Sugrue M, Dando R (2017) Participants with pharmacologically impaired taste function seek out more intense, higher calorie stimuli. Appetite 117:74-81. doi:10.1016/j.appet.2017.06.006

7) Gondivkar SM, Indurkar A, Degwekar S, Bhowate R (2009) Evaluation of gustatory function in patients with diabetes mellitus type 2. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 108:876-80. doi:10.1016/j.tripleo.2009.08.015

8) Cho H, Kim SM, Jeong SS, Kim SB (2016) Comparison of salt taste thresholds and salt usage behaviours between adults in Myanmar and Korea. Asia Pac J Clin Nutr 25:879-884. doi:10.6133/apjcn.092015.32

9) Roura E, Foster S, Winklebach A, Navarro M, Thomas W, Campbell K, Stowasser M (2016) Taste and Hypertension in Humans: Targeting Cardiovascular Disease. Curr Pharm Des 22:2290-2305

10) Hardy SL, Brennand CP, Wyse BW (1981) Taste thresholds of individuals with diabetes mellitus and of control subjects. J Am Diet Assoc 79:286-289

11) Negrato CA, Tarzia O (2010) Buccal alterations in diabetes mellitus. Diabetology Metab Syndr 15;2-3. doi:10.1186/1758-5996-2-3

12) Pavlidis P, Gouveris H, Kekes G, Maurer J (2014) Electrogustometry thresholds, tongue tip vascularization, and density and morphology of the fungiform papillae in diabetes. B-ENT 10:271-278

13) Martin B, Dotson CD, Shin YK, Ji S, Drucker DJ, Maudsley S, Munger SD (2009) Modulation of taste sensitivity by GLP-1 signaling in taste buds. Ann N Y Acad Sci 1170:98-101. doi:10.1111/j.1749-6632.2009.03920.x

14) Fournel A, Marlin A, Abot A, Pasquio C, Cirillo C, Cani PD, Knauf C (2016) Glucosensing in the gastrointestinal tract: Impact on glucose metabolism. Am J Physiol Gastrointest Liver Physiol. 310:G645-658. doi:10.1152/ajpgi.00015.2016.

15) Abbasi AA (1981) Diabetes: diagnostic and therapeutic significance of taste impairment. Geriatrics 36:73-78.

16) Naka A, Riedl M, Luger A, Hummel T, Mueller CA (2009) Clinical significance of smell and taste disorders in patients with diabetes mellitus. Eur Arch Otorhinolaringol 267:547-550. doi:10.1007/s00405-009-1123-4

17) Naik BS, Shetty N, Maben EVS (2010) Drug-induced taste disorders. Eur J Intern Med 21:240-243. doi:10.1016/j.ejim.2010.01.017

18) ASTM Standard E679-04 (2011). Standard practice for determination of odor and taste thresholds by a forced-choice ascending concentration series method of limits. ASTM [online] Available at: http://www.astm.org

19) Lawless, HT, & Heymann H (1998). Sensory evaluation of food: principles and practices. Chapman & Hall, New York, pp. 181–185

20) Bloomfeld RS, Graham BG, Schiffman SS, Killenberg PG (1999). Alterations of chemosensory function in end-stage liver disease. Physiol Behav 66:203-207

21) Borgnakke WS, Anderson PF, Shannon C, Jivanescu A (2015) Is there a relationship between oral health and diabetic neuropathy? Curr Diab Rep 15:93. doi:10.1007/s11892-015-0673-7

22) Sandberg GE, Sundberg HE, Fjellstom CA, Wikblad KF (2000) Type 2 diabetes and oral health. A comparison between diabetic and non-diabetic subjects. Diabetes Res Clin Pract 50:27-34

23) Henkin RI, Martin BM, Agarwal RP (1999) Decreased parotid saliva gustin/carbonic anhydrase VI secretion: an enzyme disorder manifested by gustatory and olfactory dysfunction. Am J Med Sci 318:380-391

24) Bromley SM (2000) Smell and taste disorders: a primary care approach. Am Fam Physician 61:427-436

25) Duda-Sobczak A, Araszkiewicz A, Urbas M, Borucki L, Kulas K, Chudzinski M, Suwalska A, Zozulinska-Ziolkiewicz D (2017) Impaired olfactory function is related to the presence of

neuropathy in adults with type 1 diabetes. Diab Vasc Dis Res 14:139-143. doi:10.1177/1479164116679079

26) Gardiner J, Barton D, Vanslambrouck JM, Braet F, Hall D, Marc J, Overall R (2008) Defects in tongue papillae and taste sensation indicate a problem with neurotrophic support in various neurological diseases. Neuroscientist 14:240-50. doi:10.1177/1073858407312382

27) Kawaguchi H1, Murata K (1995) Electric gustatory threshold in diabetics and its clinical significance. Nihon Jibiinkoka Gakkai Kaiho 98:1291-1296

28) Le Floch JP1, Le Lièvre G, Labroue M, Peynègre R, Perlemuter L (1992) Early detection of diabetic patients at risk of developing degenerative complications using electric gustometry: a five-year follow-up study. Eur J Med 1:208-214

29) Laffitte A, Neiers F, Briand L (2014) Functional roles of the sweet taste receptor in oral and extraoral tissues. Curr Opin Clin Nutr Metab Care 17:379-385

30) Gaphor SM, Saeed RA (2014) The evaluation of taste threshold for four main tastes between diabetic and healthy individuals. ESJ 10:434-439

31) Fernandez-Garcia JC, Alcaide J, Santiago-Fernandez C, Roca-Rodriguez MM, Aguera Z, Baños R, Botella C, de la Torre R, Fernandez-Real JM, Fruhbeck G, Gomez-Ambrosi J, Jimenez-Murcia S, Menchon JM, Casanueva FF, Fernandez-Aranda F, Tinahones FJ, Garrido-Sanchez L (2017) Correction: An increase in visceral fat is associated with a decrease in the taste and olfactory capacity. PloS one, 3;12:e0171204. doi:10.1371/journal.pone.0171204

32) Maliphol AB, Garth DJ, Medler KF (2013) Diet-Induced Obesity Reduces the Responsiveness of the Peripheral Taste Receptor Cells. PLoS ONE 8:e79403. Doi:10.1371/journal.pone.0079403

33) Stolbová K, Hahn A, Benes B, Andel M, Treslová L (1999) Gustometry of diabetes mellitus patients and obese patients. Int Tinnitus J 5:135-140

34) Hwang LD, Cuellar-Partida G, Ong JS, Breslin PA, Reed DR, MacGregor S, Gharahkhani P, Martin NG, Rentería ME (2016) Sweet Taste Perception is Associated with Body Mass Index at the Phenotypic and Genotypic Level. Twin Res Hum Genet 19:465-471. doi:10.1017/thg.2016.60

35) Berthoud HR, Zheng H (2012) Modulation of taste responsiveness and food preference by obesity and weight loss. Physiol Behav 107:527–532. doi:10.1016/j.physbeh.2012.04.004

36) Niki M, Jyotaki M, Yoshida R, Ninomiya Y (2010) Reciprocal modulation of sweet taste by leptin and endocannabinoids. Results Probl Cell Differ 52:101-114. doi:10.1007/978-3-642-14426-4_9

37) Domingos AI, Vaynshteyn J, Voss HU, Ren X, Gradinaru V, Zang F, Deisseroth K, de Araujo IE, Friedman J (2011) Leptin regulates the reward value of nutrient. Nat Neurosci 14:1562-1568

38) Shin YK, Martin B, Golden E, Dotson CD, Maudsley S, Kim W, Jang HJ, Mattson MP, Drucker DJ, Egan JM, Munger SD (2008) Modulation of taste sensitivity by GLP-1 signaling. J Neurochem 106:455-463. doi:10.1111/j.1471-4159.2008.05397.x

39) Östberg AL, Bengtsson C, Lissner L, Hakeberg M (2012) Oral health and obesity indicators. BMC Oral Health 12:50. doi:10.1186/1472-6831-12-50

40) Drewnowski A, Henderson SA, Levine A, Hann C (1999) Taste and food preferences as predictors of dietary practices in young women. Public Health Nutr 2:513-519

41) Sergi G, Bano G, Pizzato S, Veronese N, Manzato E (2016) Taste loss in the elderly: possible implications for dietary habits Crit Rev Food Sci Nutr 57:3684-3689. doi:10.1080/10408398.2016

42) Nordin S, Razani LJ, Markison S, Murphy C (2003) Age-associated increases in intensity discrimination for taste. Exp Aging Res 29:371-381

43) Tsujimoto T, Imai K, Kanda S, Kakei M, Kajio H, Sugiyama T (2017). Sweet taste disorder and vascular complications in patients with abnormal glucose tolerance. Int J Cardiol 221:647-641. doi: 10.1016/j.ijcard.2016.07.062

44) Te Morenga LA, Howatson AJ, Jones RM, Mann J (2014). Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. Am J Clin Nutr 100:65-79. doi: 10.3945/ajcn.113.081521

45) Dhurandhar NV, Thomas D (2015). The link between dietary sugar intake and cardiovascular disease mortality: an unresolved question. JAMA 313:959-960. doi: 10.1001/jama.2014.Mar 3;313:959-60

46) Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB (2014). Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern Med 174:516-524. doi: 10.1001/jamainternmed.2013.13563

47) Young RL, Chia B, Isaacs NJ, Ma J, Khoo J, Wu T, Horowitz M, Rayner CK (2013). Disordered control of intestinal sweet taste receptor expression and glucose absorption in type 2 diabetes. Diabetes 62:3532-3541. doi: 10.2337/db13-0581

48) Boyce JM, Shone GR (2006) Effects of ageing on smell and taste. Postgrad Med J 82:239-241.

49) Stevens JC, Cain WS (1993) Changes in Taste and Flavor in Aging. Crit Rev Food Sci Nutr 33:27-37

50) Heft MW, Robinson ME (2010) Age Differences in Orofacial Sensory Thresholds. J Dent Res 89:1102-1105. doi:10.1177/0022034510375287

51) Cowart BJ, Yokomukai Y, Beauchamp GK (1994) Bitter taste in aging: compound-specific decline in sensitivity. Physiol Behav 56:1237-1241

52) Enns MP, Hornung DE (1988) Comparisons of the estimates of smell, taste and overall intensity in young and elderly people. Chemical Senses 13:131-139

53) Salmon AB (2016) Beyond Diabetes: Does Obesity-Induced Oxidative Stress Drive the Aging Process? Antioxidants 5:24. doi:10.3390/antiox5030024

54) Anderson CA, Cobb LK, Miller ER 3rd, Woodward M, Hottenstein A, Chang AR, Mongraw-Chaffin M, White K, Charleston J, Tanaka T, Thomas L, Appel LJ (2015) Effects of a behavioral intervention that emphasizes spices and herbs on adherence to recommended sodium intake: results of the SPICE randomized clinical trial. Am J Clin Nutr 102:671-679. doi:10.3945/ajcn.114.100750

55) Mattes RD, Popkin BM (2009) Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. Am J Clin Nutr 89:1-14. doi:10.3945/ajcn.2008.26792

56) Ozcariz SG, Bernardo Cde O, Cembranel F, Peres MA, González-Chica DA (2015). Dietary practices among individuals with diabetes and hypertension are similar to those of healthy people: a population-based study. BMC Public Health 15:479. doi:10.1186/s12889-015-1801-7