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Gustatory Function in Patients with Type 1 and Type 2 Diabetes Mellitus

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ABSTRACT

This study evaluated the gustatory-function in patients with type 1(T1DM) and type 2(T2DM) diabetes compared to a control-group without diabetes, using passion-fruit juice. We studied three groups: 44 patients with T2DM, 34 with T1DM, and 73 healthy people. Detection and recognition thresholds were determined by a forced-three-alternative-choice method, with ascending concentrations (3AFC), using five basic-tastes in passion-fruit juice. The threshold values for each basic-taste in each group were calculated as the Best-Estimate-Threshold. Linear regression analysis between the threshold values, socio demographic and clinical variables, comorbidities, and complications associated with diabetes, were performed. Statistical-analysis was executed using the SAS statistical software. Results showed that neither time of diabetes nor glycated-hemoglobin (HbA1c) were correlated with the perception of bitter, sour, sweet and umami tastes.Furthermore, in T2DM, the detection-threshold of sour, umami, and bitter tastes, as well as recognition of sour, sweet, and umami tastes were worse. Individuals with T1DM had worse detection and recognition of sweet and umami tastes. Physical activity, Body Mass Index (BMI), HbA1c, insulin dose, blood glucose at the time of the test, and retinopathy were significant predictors regarding the perception of basic-tastes. Knowledge of this reduced sensitivity in the perception of basic-tastes is very important for diabetic patients and their families, as it can improve the quality of life of these patients. Conversely, the lack of this condition may result in increased intake of specific foods by patients, making it difficult to obtain good glycemic-control and predisposing to the onset of chronic diabetic complications.

Keywords: *passion fruit juice, basic tastes, threshold, T1DM and T2DM.*

INTRODUCTION

The sense of taste plays a critical role in the nutritional status. Palate can affect the individual's health by changing feeding habits, appetite, and food intake. Moreover, it participates in the regulation mechanisms involved in food acceptation and rejection, *and* protection against harmful substances intake [1, 2]

Taste sense can be modified, and these changes are classified in hypogeusia (taste decrease), ageusia (lost of taste), dysgeusia (sensation of palate change), parageusia (taste distortion by stimulus), and phantogeusia (taste distortion without stimulus). Such changes in taste perception can be triggered by the following factors: 1) problems in the taste carriers for the gustatory buds; 2) release of bad-tasting substances from the oral or nasal cavity; 3) destruction of gustatory receptors; 4) injury of the nerves that innervate the gustatory buds; and 5) central neural disorders[3,4,5,6]

Various mechanisms can contribute to the loss or change of gustatory function, such as: age, ethnicity, drug use for treating another disease, alcohol consumption, smoking, infection, poor oral hygiene, nutrients consumption deficiencies, and diseases as Alzheimer's, Parkinson's, hypothyroidism, and diabetes *mellitus*[1,3,7].

According to the International Diabetes Federation (IDF) [8], diabetes is a chronic disease that occurs when the body cannot produce enough insulin and/or cannot use it effectively. Secretory or

insulin-related disorders promote a chronic hyperglycemia state that, if not corrected in time, results in damage to several body tissues, including brain, heart, lower limbs, retina, and kidneys. Arterial vessels are the most affected by the untreated diabetes, leading to micro- and macro-angiopathies. In the presence of such complications, the diabetic patients can have great health damage since they may result in acquired blindness, kidney failure, neuropathy, and diabetic foot, in addition to stroke and myocardial infarction [8].

Type-1Diabetes *Mellitus* (T1DM), mostly triggered by autoimmune process, is mediated by regulatory T lymphocytes and results from the destruction of the insulin-secreting pancreatic β cells. In Type-2 Diabetes *Mellitus* (T2DM), in turn, there is a predominance of insulin resistance state, in which the endocrine pancreas produces insulin but not in the necessary amounts to maintain the normal levels of blood glucose. This framework characterizes resistance to insulin action on the target organs; as the disease evolves, β cells lose their secretory capacity and the compensatory mechanism is unable to keep blood glucose levels in the normal range, leading to hyperglycemia[8]

Stolbova et al. (1999)[9]and Ship (2003)[10] demonstrated that adults with diabetes could present hypogeusia or decreased gustatory perception with consequent hyperphagia and obesity, as well as inability to maintain a proper diet, interfering with the glycemic control. Lack of metabolic control over the disease can result in increased incidence and progression of complications related to the diabetes [9,10]

Available reports on the possible changes in gustatory functions of patients with T1DM and T2DM are contradictory in several aspects, justifying the need for further studies to better understand this association. In addition to that, such studies assessed the gustatory perception only in aqueous solutions instead of food arrays, which can compromise the results obtained[2].

The aim of this study was to assess the gustatory function of patients with T1DM and T2DM through the values of recognition and detection thresholds of the five basic tastes in passion fruit juice and also the possible correlations between taste dysfunctions and duration of disease, metabolic control and presence of diabetic complications.

METHODOLOGY

Subjects

This was a cross-sectional, observational study conducted with 164 subjects, aged 18 years or over, divided into three groups: 44 patients withT2DM (19 men and 25 women); 34 patients with T1DM (12 men and 23 women); and a control group with 73 individuals without diabetes (12 men and 61 women), selected and invited to participate in the study in the own Clinical Hospital, School of Food Engineering of Unicamp, and residents of Campinas (Brazil).This study was approved by the Ethics Committee of the University of Campinas number 00656812. 4.0000.5404. Written informed consent was obtained from all participants of the study. Diabetic patients were selected during a routine check-up in the specialized outpatient clinic of type 1 and 2 diabetes in the Endocrinology service of the Clinical Hospital of the University of Campinas (Campinas, Brazil) from January 2013 to July 2014.

Inclusion Criteria

Diagnoses of Type 1 or 2diabetes mellitus, in accordance with the following criteria of the American Diabetes Association (ADA)[11]: fasting blood glucose (at least 8 hours fasting) ≥ 126mg/dL (7.0mmol / L) or blood glucose test (2 hours) ≥ 200mg/dL (11.1 mmol / L) after ingestion of 75gr oral glucose; or random plasma glucose ≥ 200mg/dL (11,1 mmol / L) in the presence of 2 or more symptoms compatible to decompensated diabetes;HbA1c ≥ 6,5%, High Performance Liquid Chromatography method (HPLC)[11].

- Age ≥ from 18
- Diagnosis of T1DM or T2DM for at least 1 year;
- Being monitoredby the Endocrinology Service of Unicamp for at least 6 months.

Exclusion Criteria

- Being under 18 years old;
- Smokers or alcoholics (excessive drinkers, whose dependence on alcohol is accompanied by mental, physical, relational, and socio-economic behavioral disorders)[12];
- Being pregnant or lactating;
- Patients using immunosuppressive drugs, or organ transplant or chemotherapy or radiation because of some kind of neoplasm.

Sampling Calculation

To calculate the sample size, a comparison of the numerical variables was performed between the 3 groups, setting α to 5% and β to 20% (sample power of 80%). Variables were transformed into ranks in the calculations due to the absence of a normal variables' distribution.

This study was approved by the Ethics Committee for Research with Human Beings of the State University of Campinas (protocol No. 25968 of 05.03.2012), and the participation in the study was conditioned to reading and signing the Informed Consent Form.

Clinical and Laboratory Characteristics of the Patients with Diabetes Mellitus

The following data were obtained through research of the patients' medical records.

- Gender and Age.
- Weight (kg); height (m); BMI (Body Mass Index): calculated from the formula weight/ height^2 (kg/m^2).
- Diabetes duration (years).
- Metabolic control of the disease, obtained through the mean of the last 3HbA1c analyses, Method: Ion-exchange Column Chromatography in HPLC system, normal value: 4 – 6%.
- Treatment of Diabetes
    - Oral drugs as sulfonylureas class: glibenclamide, gliclazide, glimepiride, and insulin action amplifiers (metformin).
    - Insulin Therapies and Dosis: NHP, Regular, Insulin analogues (long-acting plus ultra-rapid analogs); dosis expressed in units/ Kg.
    - Association of oral drugs and insulin;
    - Presence of comorbidities: systemic arterial hypertension (individuals with systolic pressure >130mmHg and/or diastolic pressure > 85mmHg) (ADA, 2010)[13], dyslipidemia (changes in lipid profile, including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c)[11], thyroid dysfunction as hypothyroidism, diagnosed by decreased T4Levels (T4L), competitive chemiluminescence immunoassay method and increased levels of ultra-sensitive TSH (TSHUs), third-generation electrochemiluminometric method, or hyperthyroidism (increase levels of T4L and reduction in TSHUs levels);
    - Chronic complications of diabetes: retinopathy; nephropathy, diagnosed by the increased urinary excretion of albumin in the first morning urine (normal value: < 30 mg/g creatinine); and presence of sensory-motor peripheral neuropathy.
- Use of other drugs, unrelated to diabetes, such as: Antidepressants (Amitriptyline), antihypertensives (diuretics as furosemide and thiazides, angiotensin-converting enzyme inhibitors like captopril and enalapril, angiotensin receptor blockers such as Losartan, calcium-channel blockers as nifedipine, and beta blockers like propranolol), antiviral agents (Acyclovir and Amantadine), lipid-lowering agents (Atorvastatin and Lovastatin), pancreatic enzymes (Pancrelipase), and drugs for thyroid disorders (Levothyroxine, Propylthiouracil)[14].

Capillary Blood Glucose at the Moment of Gustatory Tests

The capillary blood glucose was evaluated at the moment of the 5-taste testing through a drop of blood obtained by index finger puncture using One-Touch® glucometer.

Covariates

Demographic variables included: educational level, marital status, and origin. Lifestyle factors assessed were: physical activity frequency (yes or no), dental prosthesis (yes or no), allergies on the respiratory system (yes or no), and digestive diseases (yes or no). Individuals who practiced some kind of physical exercise for at least 150min/week were considered physical activity practitioners [15, 13].

Stimuli

Five basic tastes were evaluated: sweet (sucralose), sour (citric acid), salty (sodium chloride), bitter (caffeine), and umami (monossodium glutamate) in passion fruit juice. For each basic taste, eight concentrations were prepared (multiplication factor of 1.6), and the passion fruit juice was prepared by diluting 1 part of concentrated juice (Da Fruta®) in 6 parts of water. **Table 1** shows the concentrations used in the five basic tastes.

Table1. *Series of dilutions for each basic taste*

Basic Taste	Sweet	Sour	Salty	Bitter	Umami
Substances	Sucralose	Citric acid monohydrate	Sodium chloride	Caffeinean hydrous	Monossodium glutamate
M (mol/L)	58.44	194.19	210.14	397.64	187.13
Dilution (mM)					
D1	3.5934	0.2013	3.7475	0.0065	1.0153
D2	5.8179	0.3218	5.9960	0.0105	1.6245
D3	9.2402	0.5149	9.5936	0.0168	2.5992
D4	14.8870	0.8239	15.3497	0.0266	4.1586
D5	23.9561	1.3182	24.5593	0.0427	6.6541
D6	38.3299	2.1092	39.2952	0.0684	10.6466
D7	61.2594	3.3750	62.8723	0.1096	17.0346
D8	98.0492	5.3998	100.5963	0.1755	27.2553
Dilution (g/L)					
D1	0.2100	0.0391	0.7875	0.0026	0.1900
D2	0.3400	0.0625	1.2600	0.0042	0.3040
D3	0.5400	0.1000	2.0160	0.0067	0.4864
D4	0.8700	0.1600	3.2256	0.0106	0.7782
D5	1.4000	0.2560	5.1609	0.0170	1.2452
D6	2.2400	0.4096	8.2575	0.0272	1.9923
D7	3.5800	0.6554	13.2120	0.0436	3.1877
D8	5.7300	1.0486	21.1393	0.0698	5.1003

All solutions were prepared the day before the test and store at 3°C. They were kept and room temperature during the test. Tasters were given 20ml of each stimulus in plastic cups, coded with 3-digit numbers.

Threshold

Detection and recognition thresholds, for all basic tastes, were assessed according to the *three-alternative-forced-choice* (3AFC), with ascending concentration [16]. Detection threshold is the lowest concentration at which each basic taste can be detected. The taster can only detect the presence of a basic taste but cannot identify the quality. Recognition threshold is the lowest concentration at which each taste can be recognized. In this threshold, the taster can notice the quality of the taste evaluated [16].

To each of the volunteer, eight triads were presented in each session with minimum interval of 15 min between each presentation. Each triad was formed with two blanks (with only passion fruit juice) and one test sample (with passion fruit juice and basic taste). Within each set, the assessors were asked to indicate that sample which is different from the two others (detection threshold) or which exhibits a recognizable stimulus (recognition threshold). If the subject was unable to identify the taste, another row with the next higher concentration of the taste solution with passion fruit juice was presented [16].

According to ASTM (2011) [16], Detection Threshold (DT) is the lowest concentration of a stimulus (basic taste) is detected as determined by the best estimate criterion. And, Recognition Threshold (RT) is the lowest concentration of a stimulus (basic taste) is recognized as determined by the best-estimate criterion [16, 17]

The tests are completed when the panelist either completes the evaluation of all concentrations of the scale, or reaches a set wherein the test sample is correctly identified, then continues to choose correctly in higher concentration test sample sets [16].

The order of presentation of samples in each triad was balanced to eliminate positional bias, and the concentrations each basic taste were presentation in ascending order. The values were calculated as *Best Estimate Criterion* [18, 16].

Data Evaluation and Statistical Analysis

The best estimate criterion was used to calculate the individual threshold; it is an interpolated concentration value, but not necessarily the concentration value that was actually presented. In this practice it is the geometric mean of the last missed concentration and the next (adjacent) higher concentration16. The best estimate threshold concentration for the volunteer is then the geometric mean of that concentration at which the last miss occurred and the next higher concentration was identified [16].

For those subjects who were correct at the lowest concentration, their individual BET was estimated as the geometric mean of the lowest

concentration and the hypothetical next lower concentration that would have been given had the series been extended. And for those who cannot identify/recognize the basic taste at the highest concentration, their individual BET was estimated as the geometric mean of the highest concentration tested in the study and the next concentration that have been given had the series been extended. The group BET for each basic taste was calculated as the geometric mean of the individual BET. Standard deviation log10 provided a measure of the group´s variation [18, 16].

To describe the sample profile according the studied variables, tables of frequency were devise for the categorical variables, with values for absolute frequency (n) and percentage (%); in addition, description statistics of the numeric variables were performed, including values for mean, standard deviation, minimum and maximum values, and median.

To compare the taste perception results among groups the variance analysis (ANOVA) was performed followed by a Tukey post-hoc test ($p \leq 0.05$) to identify the differences between them. For analyzing the relation between the factors studied and the results on taste perception, a linear regression analysis was used. The variables were transformed into ranks due to the absence of a normal distribution.

For comparing the taste perception results regarding glycemic values at the moment of the tests and glycated hemoglobin rates between the two diabetics groups, Kruskal-Wallis test was used. When the test showed a significant difference, the Dunn post-hoc test was used to identify this difference.

The software SAS (2008)[19] was used for statistical analysis.

RESULTS

Clinical, Laboratory, and Socio-Demographic Characteristics

Clinical, laboratory, and socio-demographic characteristics of each groups are described in **Table 2**.

Table2. *Socio-demographic and clinical profile of the T1DM, T2DM and control groups*

	DM1 n=35	DM2 n=44	Control n=73	P value
Gender Female	23 (65.71%)	25 (56.82%)	61 (83.56%)	**0.0053**
Idade (anos)	32.54 ± 7.03	57.14 ± 5.25	37.34 ± 14.10	**<0.0001**
Duration of diabetes (years)	14.56 ± 8.97	19.49 ± 8.71	------	
BMI (kg/m^2)	26.36 ± 5.54	31.22 ± 6.99	24.65 ± 4.38	**<0.0001**
HbA1c (%) **<7.0%** **>7.0%**	 4 (11.42%) 31 (88.57%)	 8 (18.18%) 36 (81.82%)	 ------- -------	
Capillary blood glucose test (mg/dL) in the moment of test	190.29(52.86)	189.16(64.85)	121.26(33.77)	
Education **Elementary school** **Hight school** **Higher education**	 5 (14.27%) 25 (71.42%) 5 (14.27%)	 26 (60.46%) 10 (23.25%) 7 (16.28%)	 7 (9.71%) 18 (24.99%) 47 (65.27%)	
Civil status **Single** **Married** **Divorced** **Widower**	 20 (57.14%) 11 (31.42%) 3 (8.57%) 1 (2.86%)	 5 (11.62%) 32 (74.41%) 2 (4.65%) 4 (9.30%)	 37 (50.68%) 30 (41.09%) 1 (1.36%) 5 (6.84%)	
Frequency of physical activity	16 (45.71%)	26 (59.09%)	45 (61.64%)	0.2809
Dental prosthesis	10 (28.57%)	35 (81.40%)	17 (23.29%)	**<0.0001**
Allergy of upper respiratory tract	13 (30.95%)	8 (22.86%)	11 (15.07%)	0.1306
Digestive disorders	17 (39.53%)	4 (11.43%)	13 (17.81%)	**0.0068**
Hypertension	17 (50.00%)	39 (88.64%)	4 (5.48%)	**<0.0001**
Dyslipidemia	19 (55.88%)	37 (84.09%)	6 (8.22%)	**<0.0001**
Thyroid dysfunctions	12 (35.29%)	10 (22.73%)	7 (9.59%)	**0.0056**

The data are means ± SD (standard deviation) or number of responses (percentage)

Female gender prevailed in all evaluated groups (56.8%; 65.7% e 83.6%, for T1DM, T2DM, and control group, respectively), with significant difference ($p<0.05$). Of the 44 patients with T2DM, 32 (74.41%) were married and 60.46% had only elementary school education. In contrast, 31.42% of those with T1DM were married and 71.42% were attending high school. The mean age of the group T2DM (57.14 ± 5.25) was higher ($p<0.001$) than in the other

groups: 32.54 ± 7.03 and 37.34 ± 14.10 for T1DM and control group, respectively.

Regarding Body Mass Index (BMI) and the use of dental prosthesis, both were higher in patients with T2DM (31.22 ± 6.99 e 81.40%) when compared to T1DM (26.36 ± 5.54 e 28.57%) and control (24.65 ± 4.38 e 23.29%) groups.

Both diabetics groups showed values of glycated Hemoglobin higher than 7% (T1DM: 8.2% e T2DM: 8.8%), pointing to an inappropriate metabolic control of the disease.

Analyzing the means of capillary blood glucose performed at the time of the tests, we could observe very similar values between the 2 diabetics groups (about 190mg/dL). In the control group, this mean was 121.3 ± 33.8, a value considered normal since the individuals were not in 8-hour fasting.

Regarding Body Mass Index (26.36 ± 5.54; 31.22 ± 6.99 e 24.65 ± 4.38), use of dental prosthesis (28.57%, 81.40% e 23.29%), digestive disorders (39.53%, 11.43% e 17.81%), hypertension (50.00%, 88.64% e 5.48%), dyslipidemia (55.88%, 84.09% e 8.22%), and thyroid dysfunctions (35.29%, 22.73% e 9.59%) there was a significant difference between the groups evaluated (T1DM, T2DM, and control groups, respectively).

Regarding chronic complications of diabetes mellitus, it was observed that there was no significant difference between T1DM and T2DM groups, according to what can be seen in **Table 3.**

Table3. *Comorbidities and chronic complications of Diabetes Mellitus*

	DM1 n=35	DM2 n=44	P-value
Retinopathy	19 (55, 88%)	20 (45,45%)	0,3611
Nephropathy	20 (58, 82%)	23 (52,27%)	0,5641
Neuropathy	13 (38, 24%)	18 (40,91%)	0,8109
Peripheral vascular disease	0 (0, 00%)	3 (6,82%)	0,2527
Acutemyocardialinfarction	0 (0, 00%)	3 (6,82%)	0,2527

The data are shown in number of responses (percentage)

Comparative Threshold Data for the Five Basic Tastes between T1DM, T2DM, and Control Group

Results of **Table 4** show the threshold values, compared between T1DM, T2DM, and control groups. Initially, the evaluation of these data was made without adjustments, which were then made regarding the following variables: age, gender, use of medications as anti-hypertensive and anti-dysplidemic drugs, and for thyroid treatment, among others. Such adjustment was necessary since the patients' age, use of drugs, and the predominance of female gender in the 3 groups could interfere with the results, regardless the presence of Diabetes Mellitus.

Table4. *Comparative threshold data for the five basic tastes between T1DM, T2DM, and control group without adjustments and with adjustments for age, gender, use of medications.*

Basic Tastes	DM1 n=35 g/L	DM2 n=44 g/L	Control n=73 g/L	P-value*	P-value adjustments**
Salt					
Detection	0.83(0.59)	1.32(1.22)	0.94(0.65)	**0.0409**[c]	0.3372
Recognition	1.23(0.62)	1.86(1.26)	1.30(0.70)	**0.0058**[bc]	0.0804
Bitter					
Detection	0.20(0.12)	0.42(0.33)	0.25(0.23)	**0.0014**[bc]	0.2476
Recognition	0.38(0.30)	0.55(0.33)	0.34(0.24)	**0.0021**[bc]	**0.0033**[bc]
Acid					
Detection	1.93(1.54)	2.94(2.80)	1.53(1.00)	**0.0011**[bc]	**0.0008**[bc]
Recognition	2.80(1.82)	3.64(3.18)	1.98(1.26)	**0.0004**[bc]	**0.0002**[b]
Sweet					
Detection	0.01(0.01)	0.01(0.01)	0.02(0.04)	**0.0356**[a]	**0.0282**[a]
Recognition	0.02(0.01)	0.01(0.01)	0.02(0.05)	**0.0003**[a]	**0.0063**[ab]
Umami					
Detection	0.72(0.61)	1.06(1.30)	0.48(0.47)	**0.0102**[a]	**0.0035**[ab]
Recognition	1.23(1.07)	1.63(1.37)	0.72(0.53)	**0.0001**[b]	**0.0175**[ab]

*The data are means ± SD (standard deviation) *p-value for data without adjustments, **p-value for data with adjustments for age, gender, use of medications.*

[a]T1DM vs. control group; bT2DM vs. control group; cT1DM vs. T2DM

Individuals with T2DM had less ability recognize bitter, sour, sweet, and umami tastes and less detection of sour and umami tastes in passion fruit juices when compared to the patients with T1DM. However, regarding the recognition of bitter taste and detection of sour taste, individuals with T2DM shown considerably higher values ($p<0.05$) than those with T1DM.

Data on **Table 4** show the decrease sensitivity of type-1 diabetics regarding sweet (recognition and detection) and umami tastes (recognition) in the passion fruit juice.

Salty (detection and recognition) and bitter (detection) tastes were the only ones that had no significant difference between the groups evaluates, when considering the adjusted data for age, gender, and medication use (Table 4.)

Multivariate Analysis of Basic Tastes Perception Regarding BMI, Hba1c, DM Duration, Capillary Blood Glucose at the Moment of the Test, Physical Activity, Diabetes Complications, and Insulin Therapy for T1DM, T2DM, and Control Groups.

The linear regression analysis of the threshold results for the five basic tastes compared to the IMC, glycated hemoglobin, disease duration, capillary blood glucose at the time of the test, physical activity, complications of diabetes, and insulin therapy regarding the 3 studied groups: T1DM, T2DM, and control, are arranged in **Tables 5a, 5b, 5c, 5d and 5e.**

Table5a. *P-value for the linear regression analysis of the threshold results for the salt taste compared to the IMC, glycated hemoglobin (HbA1c), disease duration, capillary blood glucose at the time of the test, physical activity, complications of diabetes, and insulin therapy regarding the 3 studied groups: T1DM, T2DM and control*

Variables	DM1 n=35		DM2 n=44		Control n=73	
	DT	RT	DT	RT	DT	RT
BMI (kg/m^2)	0,7837	0,3661	0,3266	0,0929	0,7843	0,9502
HbA1c	0,9153	0,9449	0,5070	**0,0315**	-----	-----
Duration of diabetes (years)	0,7402	0,5873	0,3217	0,5720	-----	-----
Capillary blood glucose test (mg/dL) in the moment of the test	0,3520	0,0868	0,7644	0,7329	0,2978	0,1896
Frequency of physical activity	**0,0005**	**0,0240**	0,0831	0,6271	0,6853	0,5972
Retinopathy	0,5771	0,1782	0,1309	0,0877	-----	-----
Nephropathy	0,6794	0,9780	0,4305	0,3517	-----	-----
Neuropathy	0,6785	0,2405	0,3891	0,5073	-----	-----
Basal Insulin (NPH) (units/Kg)	0,2136	0,2780	**0,0359**	0,5618	-----	-----
Bolus Insulin (Regular) (units/Kg)	0,0847	0,1341	0,3313	0,6812	-----	-----
Total Insulin Dose (units/Kg)	0,468	0,345	0,531	0,890	-----	-----

DT = Detection Threshold, RT= Recognition Threshold–Salt Taste

Table5b. *P-value for the linear regression analysis of the threshold results for the bitter taste compared to the IMC, glycated hemoglobin (HbA1c), disease duration, capillary blood glucose at the time of the test, physical activity, complications of diabetes, and insulin therapy regarding the 3 studied groups: T1DM, T2DM and control*

Variables	DM1 n=35		DM2 n=44		Control n=73	
	DT	RT	DT	RT	DT	RT
BMI (kg/m^2)	**0.0239**	**0.0091**	0.5989	0.9702	0.7020	0.2222
HbA1c	0.8850	0.1798	0.3626	0.8758	-----	-----
Duration of diabetes (years)	0.7326	0.1074	0.9679	0.6066	-----	-----
Capillary blood glucose test (mg/dL) in the moment of the test	0.6893	0.8393	0.7251	0.5996	0.3354	0.3155
Frequency of physical activity	0.9053	0.6060	0.8986	0.9941	0.6453	0.4080
Retinopathy	0.9779	0.2507	**0.0374**	0.0999	-----	-----
Nephropathy	0.3543	0.4857	0.9648	0.8802	-----	-----
Neuropathy	0.9821	0.9671	0.0996	0.2434	-----	-----
Basal Insulin (NPH) (units/kg)	0.8592	0.2768	0.3149	0.5555	-----	-----
Bolus Insulin (Regular) (units/kg)	0.8270	0.2704	0.8055	0.9616	-----	-----
Total Insulin Dose (units/kg)	0.9180	0.9090	0.545	0.2882	-----	-----

DT = Detection Threshold, RT= Recognition Threshold – Bitter Taste

Table5c. *P-value for the linear regression analysis of the threshold results for the sour taste compared to the IMC, glycated hemoglobin (HbA1c), disease duration, capillary blood glucose at the time of the test, physical activity, complications of diabetes, and insulin therapy regarding the 3 studied groups: T1DM, T2DM and control*

Variables	DM1 n=35		DM2 n=44		Control n=73	
	DT	RT	DT	RT	DT	RT
BMI (kg/m^2)	0.1457	0.4758	0.0639	0.0969	**0.0315**	**0.0054**
HbA1c	0.5002	0.5482	0.2983	0.2125	-----	-----
Duration of diabetes (years)	0.7809	0.9409	0.4590	0.9446	-----	-----
Capillary blood glucose test (mg/dL) in the moment of the test	0.6650	0.8786	0.1128	0.2983	0.9025	0.3660
Frequency of physical activity	0.2839	0.2601	0.4036	**0.0166**	0.8529	0.2666
Retinopathy	0.2014	0.3000	0.7731	0.9612	-----	-----
Nephropathy	0.7048	0.3816	0.4913	0.1869	-----	-----
Neuropathy	0.3581	0.4845	0.7416	0.1115	-----	-----
Basal Insulin (NPH) (units/kg)	0.5859	0.1350	0.9673	0.2797	-----	-----
Bolus Insulin (Regular) (units/kg)	0.9043	0.3282	0.4039	0.8739	-----	-----
Total Insulin Dose (units/kg)	**0.0410**	0.2360	0.512	0.8530	-----	-----

DT = Detection Threshold, RT= Recognition Threshold– Sour Taste

Table5d. *P-value for the linear regression analysis of the threshold results for the sweet taste compared to the IMC, glycated hemoglobin (HbA1c), disease duration, capillary blood glucose at the time of the test, physical activity, complications of diabetes, and insulin therapy regarding the 3 studied groups: T1DM, T2DM and control*

Variables	DM1 n=35		DM2 n=44		Control n=73	
	DT	RT	DT	RT	DT	RT
BMI (kg/m^2)	0.8557	0.8612	0.8627	0.9870	0.3527	0.2444
HbA1c	0.6154	0.9870	0.9861	0.2607	-----	-----
Duration of diabetes (years)	0.0731	0.0624	0.1955	0.1049	-----	-----
Capillary blood glucose test (mg/dL) in the moment of the test	0.6467	0.2865	0.8224	0.7479	0.9646	0.4851
Frequency of physical activity	0.4437	0.3993	0.5531	0.2056	0.9761	0.8797
Retinopathy	0.1318	0.2061	0.2733	0.8509	-----	-----
Nephropathy	0.5616	0.5101	0.9001	0.9508	-----	-----
Neuropathy	0.6879	0.1017	0.1528	0.8054	-----	-----
Basal Insulin (NPH) (units/kg)	0.6649	0.2131	0.5549	0.5922	-----	-----
Bolus Insulin (Regular) (units/kg)	0.8274	0.1166	0.5840	0.2838	-----	-----
Total Insulin Dose (units/kg)	0.5450	0.6020	0.4950	0.649	-----	-----

DT = Detection Threshold, RT= Recognition Threshold– Sweet Taste

Table5e. *P-value for the linear regression analysis of the threshold results for the umami taste compared to the IMC, glycated hemoglobin (HbA1c), disease duration, capillary blood glucose at the time of the test, physical activity, complications of diabetes, and insulin therapy regarding the 3 studied groups: T1DM, T2DM and control*

Variables	DM1 n=35		DM2 n=44		Control n=73	
	DT	RT	DT	RT	DT	RT
BMI (kg/m^2)	0.9131	0.4135	0.6867	0.5425	**0.0194**	
HbA1c	0.8315	0.9789	0.8905	0.6404	-----	-----
Duration of diabetes (years)	0.7007	0.6361	0.9215	0.8254	-----	-----
Capillary blood glucose test (mg/dL) in the moment of the test	0.5206	0.7480	**0.0439**	0.0697	0.4655	
Frequency of physical activity	0.5589	0.6404	0.2182	0.3674	0.1274	
Retinopathy	0.5874	0.8411	**0.0228**	**0.0192**	-----	-----
Nephropathy	0.9620	0.8790	0.4835	0.5751	-----	-----
Neuropathy	0.8344	0.0638	0.4036	0.7993	-----	-----
Basal Insulin (NPH) (units/kg)	0.5759	0.7724	0.9434	0.2824	-----	-----
Bolus Insulin (Regular) (units/kg)	0.5072	0.5409	0.5621	0.1460	-----	-----
Total Insulin Dose (units/kg)	0.4130	0.3390	0.3410	0.2670	-----	-----

DT = Detection Threshold, RT= Recognition Threshold–Umami Taste

Univariate regression of the variables showed that the practice of physical activity was a significant and positive predictor for salty taste (**Table 5a**) (p=0.0005 for detection and p=0.0240 for recognition) in individuals with T1DM and for sour taste (**Table 5c**) (p=0.0166 for recognition) in T2DM, indicating that patients in these groups who did not exercise regularly detected less salty taste and recognized less the salty and sour tastes.

Similarly, BMI was a positive significant predictor for gustatory perception of bitter taste in T1DM (**Table 5b**) (p=0.0239 for detection and p=0.0091 for recognition); however, it was a negative predictor for sour (**Table 5c**) (p=0.0315 for detection and p=0.0054 for recognition) and umami (**Table 5e**) (p=0.0194 for detection and p=0.0093 for recognition) tastes in the control group.

Time of diabetes and HbA1c rates were not significantly correlated to the perception of basic bitter, sour, sweet, and umami tastes in the groups evaluated.

Similarly, for the recognition of salty taste in type-2 diabetic patients, the HbA1c rates were significantly positive predictors (**Table 5a**) (p = 0.0315) for the threshold values, indicating that the smaller the HbA1c value, less the ability to recognition of salty taste in this group of patients.

Retinopathy was a significant negative predictor for recognition of umami (**Table 5e**) (p=0.0228) and sour (**Table 5b**) (p=0.0374) tastes, and for the detection of umami taste (**Table 5e**) (p=0.0192) by patients with T2DM using passion fruit juice.

Concerning insulin therapy, basal insulin treatment was a positively significant predictor only for the detection of salty taste (**Table 5a**) (p=0.0359) in passion fruit juice in patients with T2DM. Thus, it is possible to infer that patients who do not use basal insulin have a higher tendency towards recognition of salty tastes. When evaluating the total insulin dose, it was observed that it positively predicted the sour taste detection threshold in passion fruit juice in patients with T1DM. This result shows that, the higher the insulin doses used in the diabetes treatment, the greater the difficulty in detecting sour taste.

Capillary blood glucose values at the time of testing revealed that this is a significant predictor for the umami taste in passion fruit juice. This indicates that the greater the capillary blood glucose, the smaller the ability to detect umami taste for patients with T2DM (**Table 5e**) (p=0.0439) and the smaller the ability to recognize this taste for individuals in the control group (Table 5e) (p=0.0077).

DISCUSSION

The occurrence of alterations in the gustatory function can be associated to several factors, including age, alcohol consumption, smoking, infection, poor oral hygiene, nutritional deficiencies, allergies, allergic rhinitis/sinusitis, pharmacological or surgical interventions, and diseases such as Alzheimer's disease, Parkinson's, hypothyroidism, and diabetes mellitus [1, 3, 6, 7]. Therefore, this study aimed to analyze the possible changes regarding taste, using passion fruit juice in patients with T1DM and T2DMcompared to the control group.

In all three groups there was a predominance of females, and T2DM differed significantly from T1DM regarding age, BMI, oral changes, presence of other diabetes-related diseases, and use medications other than those directed to the diabetes treatment. Many of these differences, already expected, especially because of the distinctive etiopathogenesis of both DM types, were also identified regarding the control group.

Metabolic control, expressed by the average of the last three HbA1c rates, as well as the capillary blood glucose performed at the moment of testing, were very similar in both diabetics groups, showing inadequate metabolic control of the disease.

The comparison between threshold values between T2DM, T1DM, and control groups after data adjustment showed that the use of drugs for hypertension, dyslipidemia, and thyroid dysfunction treatments can interfere with the ability of recognizing bitter, sour, sweet, and umami tastes and of detecting sour and umami tastes for type-2 diabetic patients. The possible interference was studied by Naik et al. (2010)[14], whose results were similar to those of this study, in which there is a high percentage of diabetic patients using medication to control the comorbidities associated with DM.

Concerning salty taste, there was no difference between the three groups studied. These findings were also described by Lawson et al. (1979) and Le Floch et al. (1989) [20] when comparing patients with T2DM and control group.

However, Gondivkar et al. (2009) [2], Isezuo et al. (2008) [21] and Okoro, et al. (2002) [22] showed a significant difference in the perception

of salty taste among patients with T2DM and control group.

The results of this study are not in agreement with the latter authors regarding the recognition and detection of salty taste. Such fact can be explained by the use of passion fruit to present the samples, unlike the cited studies, whose authors used aqueous solutions. Passion fruit juice has features that might modify the perception of salty taste. This fruit can chemically interact and alter the taste perception. According to Keast; Breslim (2002) [23], mixtures with sour and salty features symmetrically affect the intensity of both tastes, with enhancement at low concentrations and suppression or no effect at higher ones.

Furthermore, Breslim; Beauchamps (1997)[38] reported that salts containing sodium are considered basic taste enhancers since they selectively act in suppressing compounds such as bitter and, sometimes, sour tastes, and stimulating others, such as sweetness.

On the above, it is possible that the detection of salty taste has not presented any significant difference between the groups T1DM, T2DM, and control, due to the interaction between salty taste, from the NaCl, and sour taste, from the citric acid in the passion fruit juice.

This also applies to the bitter taste because, according to Keast; Breslim (2002) [23], the low-intensity mixture between sour and bitter tastes can enhance the intensity of them, resulting in a more intense sour taste. This is a pronounce characteristic of acid fruit juices such as passion fruit.

The patients with T1DMshowed a reduced sensibility in detecting and recognizing sweet and umami tastes in passion fruit when compared to the control group. This finding is consistent with those found by Khobragade et al. (2012) [1] when evaluating patients with T1DM, they showed deterioration in the basic tastes sensibility in aqueous solutions, especially for sweet taste, compared to the control groups. One of the hypothesis for such decrease in sensitivity, especially for the sweet taste, may be due to these patients' greater intake of foods and drinks with a high content of sucrose and similars (sweeteners) in their compositions. Increased consumption of these kind of foods and drinks with high sucrose/sweeteners content can also result in a greater difficulty to achieve glycemic control [1, 2].

The exact mechanism by each both T1DM as T2DM reduce the taste perception is not fully known yet, but one of the hypothesis would be that this happens due to ainherent or acquired defect of the gustatory receptors and of peripheral neuropathy, which would affect the gustatory nerves. Neuropathy is a complication of diabetes and can be peripheral, sensory-motor or autonomic; the latter harms the sympathetic and parasympathetic systems, being also associated with teeth loss in these patients [24].

Another hypothesis would be related to the presence of microangiopathy, a frequent complication in diabetic patients with long time of disease and poor metabolic control, factors which were present in both DM groups. Thus, microangiopathy could alter the taste and promote these gustatory changes [2].

A study conducted by Pai et al. (2007) [25] evaluated the relationship between changes of the taste caused by DM and innervation and morphological changes in the taste buds. To do so, the authors studied the valved papillae of rats with DM (the disease was induced in these mice through Streptozotocin (STZ), which causes the death of pancreatic β cells). Innervation of valved papillae and gustatory taste buds of the mice with DM and the control group were detected. Results showed no significant difference in the size of the papillae between control and diabetic groups, but there was a smaller number of gustatory buds in each papilla (per animal). The quantification of gustatory buds innervation in the diabetic rats supported the visual evaluation of immune histo chemistry that the gustatory cells innervation was considerably reduced in diabetic animals. Such results suggest that the gustatory deficiency in diabetic individuals can be cause by neuropathic defects and/or morphological changes in the gustatory buds [25].

The univariate regression analysis between basic tastes perception and studied variables showed that BMI is a significant predictor of gustatory perception (**Tables 5c** and **5e**). This result is in accordance with the study of Naka et al. (2010), a can be justified by the fact obesity is on of the trigger factors of dysgeusia, regardless DM presence, as the proper taste detection can be associated with the satisfaction on food intake and, consequently, decreased taste detection can be one of the mechanisms for obesity development [9].

Stolbová et al. (1999) [9] evaluated 73 patients with T2DM, 11 with T1DM, 12 obese individuals (Body Mass Index ≥ 30) without DM, and a

control group (without diabetes and obesity) containing 29 volunteers. All individuals were subjected to a electric gustatory examination. During this exam, the electrical threshold were obtained by stimulating various regions of the tongue. According to the tests performed, hypogeusia was observed in 40% of the patients with T2DM, 33% of those with T1DM, and in 25% of the group of obese people without DM. In the control group, there was not any individual with hypogeusia. Concerning ageusia, it was observed in 5% of the patients with T2DM, 3% of those with T1DM, 14% of the obese individuals, and was not found in the control group. Given this, the authors suggested that the decrease gustatory detection (hypogeusia or ageusia) in individuals with DM can result in a situation of both hyperphagia and obesity [9].

Thus, more studies are necessary to clarify if obesity is the cause of the decreased gustatory perception or a complication of the hypogeusia/ ageusia framework present in diabetic patients. This cause-and-effect relationship is difficult to understand since the gustatory perception is only one of the many factors related to the pathophysiology of obesity, as well as of the individuals' food choices or preferences [26].

Contradictory results have been found regarding the relation between BMI and threshold. According to Donaldson et al. (2009) [26], people with high BMI may have a greater difficulty to recognize satiety and stop feeding, especially when they perform concomitant activities at the mealtimes, not paying attention to the taste of what is being ingested. It is possible that some change in taste perception may alter the attention for an specific taste [26].

The positive association between physical activity practice and glycemic control influenced in the better gustatory perception observed by this study. Similar results were found by Nichols et al. (2000) [27] and Loprinzi et al. (2014) [28].

Concerning HbA1c rates and salty taste recognition threshold values, we observed that the smaller the HbA1c value, the smaller the ability to recognize such taste. This result is consistent with those reported by Gondivkar et al. (2009) [2].

Concerning the total insulin dose, we verified that it is a significant predictor for acid taste detection threshold, suggesting that the higher the insulin dose used in the diabetes treatment, the greater the difficulty in detecting the taste. This inverse correlation was also reported by Yoshida (2012) [29] and Baquero; Gilbertson (2011) [30] in experimental studies in mice.

In these studies, Yoshida (2012) [29] and Baquero; Gilbertson (2011) [30]have demonstrated that insulin can affect sensibility to salt. The epithelial sodium channel (ENaC) is essential for water and electrolyte balance, and is believed to be a salty taste receptor. However, the ENaC can be inhibited by amiloride and/or benzamil and its function can be modified by several hormones, including insulin, whose function is to activate ENaC channels in the apical membrane of taste cells. Therefore, insulin, when administered in the taste buds, activates the ENaC, thus increasing the mice sensibility to salty tastes. These results may partly explain why diabetic patients who used basal insulin showed a higher ability to recognize salty taste when compared to those patients who did not use insulin therapy [29, 30].

Capillary blood glucose values at the time of testing revealed that this is a significant predictor for the umami taste in passion fruit juice, indicating that the greater the capillary blood glucose, the smaller the ability to detect umami taste for patients with T2DM and smaller the ability to recognize this taste for individuals in the control group. These findings are consisted with those of Gondvikar et al. (2009) [2] and Le Floch et al. (1989)[31].

Kawagushi; Murata (1995)[32]studied the relation between the electric gustatory threshold of diabetic patients regarding age, time of disease, and diabetic complications. Patients with longer time of disease had higher electrical gustatory threshold. This correlation was not observed in this study. The same authors concluded that the elevation of electric gustatory taste threshold in diabetic individuals arose before the beginning or in the earliest stage of DM complications (neuropathy, retinopathy, and nephropathy), and this threshold increased as the complications progressed. Thus, electric gustatory threshold can be considered and extremely useful indicator to prevent diabetic complications since it allows detecting the three main diabetic complication already in their early stages.

Despite the findings in our study correlating basic tastes thresholds and metabolic control parameters, Wasalathanthri et al. (2014) [33] state that each individuals' response to sensory stimuli (basic tastes) cannot be considered as

static because they are influence by many factors such as body weight changes and different levels of neurotransmitters, especially serotonin and noradrenaline. Both are associated with the nerve impulses responsible for the tastes/flavors perception. According to the same authors, anxiety and depression states can coincide with oscillations on these neurotransmitters' levels. The presence of these changes in diabetic patients or patients with both diabetes and other diseases could partly explain the appearance of taste-related disorders.

Time of disease and glycated hemoglobin rates (HbA1c) were not significant predictor factors for bitter, sour, sweet, and umami tastes. This study results agree with those described by Naka et al. (2010)[34], Le Floch et. al. (1992)[31], Perros et al. (1996)[35]and Siddiqui et al. (2014)[36].

According to Naka et al. (2010), most diabetic patients, especially those with T2DM, are not evaluated for gustatory and olfactory changes, especially those related to harm in these functions [34].

On the above, it can be assumed that the diagnosis and knowledge of gustatory sensibility in diabetic patients could assist in relevant issues regarding choices, consumption, and quantities of food ingested. An immediate implication of such knowledge would be the possibility of orientations and prevention of ingesting high amounts of sodium or sucrose due to the lower gustatory sensibility of these foods [2, 31, 34].

It is important to note the type of feeding array used, which is relevant to the assessment of gustatory perception. Studies available in the literature used aqueous solutions to describe the changes related to this perception. Thus, the results cannot be extrapolated to other types of foods, because when they are inserted into any feeding array they can result in interaction between these substances, suppressing or exacerbating the perception and recognition of some taste. Thus, the effect of each substance in the final quality of gustatory perception is variable and should be evaluated considering such variables [37].

In conclusion, patients with diabetes presented changes in tastes, both concerning recognition as detection. There is damage in the gustatory function of type 2 diabetic patients mainly regarding bitter, sour, sweet, and umami tastes in passion fruit juice, while in T1DM patients these changes occurred in sweet and umami tastes. Probably, the greatest harm in the gustatory function of patients with T2DM is due to the greater duration and presence of diabetic related diseases, and the use of many drugs that can interfere in it. The diagnosis and knowledge on the reduction of basic tastes perception sensitivity, both by the diabetics as by their families, is extremely important, as it interferes in food choices and consumption, which may result in weight gain, increased difficulty in obtaining glycemic control and, thus, emergence of chronic complications of diabetes, with decreased quality of life.

Study Limitations

The comparability between the results found in the literature and those of our study is limited since the basic tastes threshold values are different in passion fruit juice and aqueous solutions. In addition, the assessment of capillary blood glucose at the moment of the test may have wide variations throughout the day.

Finally, the volunteers might have found it difficult to recognize the umami, as the Brazilian population is not yet fully acquainted with this basic taste in comparison to the others (sweet, salty, bitter, and sour).

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