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Recognition of taste in patients during antineoplastic therapy with platinum drugs

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ABSTRACT

Taste changes caused by the use of platinum drugs have been described. However, few studies qualify the impaired tastes and whether these changes are derived exclusively from chemotherapy (QTx).
Aims: Evaluation of changes in sweet, sour, salty, bitter, and umami tastes in patients receiving QTx with platinum drugs was the aim of this study.
Methods: A total of 43 subjects, 21 from the study group and 22 from the control, were studied in two time periods, one before the start of QTx (T0) and another after two cycles of QTx (T1). The usual dietary intake, body mass index (BMI), handgrip strength and fatigue (through the fatigue pictogram) were evaluated to characterize the group studied. Taste Strips tests were performed for all 4 tastes and umami was studied by comparing Likert's scale using monosodium glutamate (GMS) food. Statistical analysis was performed using repeated measures (ANOVA), mixed model, with significance level $p \leq 0.05$.
Results: Salty and sour were the most affected tastes in the study group ($p = 0.001$ and 0.05); as well as the ionotropic receptors ($p = 0.02$) responsible for identifying these tastes. There was a difference between the times for BMI, dynamometry and impact in daily activities, by the fatigue pictogram ($p = 0.008$, 0.009 and 0.006 respectively).
Conclusion: These findings suggest an important role in altering taste recognition, mainly in salty and sour tastes, identified by ionotropic receptors, which seems to be related to dietary changes. QTx has demonstrated a contribution to impairment of functionality and fatigue.

Introduction

Transformations in the diet of cancer survivors are evident to themselves, their family, and health professionals; weight loss processes associated with these changes contribute to patients having a worse nutritional status and poorer quality of life and depend on their tolerance to antineoplastic therapy [1]. The biochemical process of identifying a particular taste is not yet well understood [2]. Cells involved in taste identification are bipolar and have a fine epithelial dendritic process, which can either be isolated or grouped and packed in papillae and have an average life of 10 d [3]. The papillae are distributed in the oral cavity in the epiglottis, palate, pharynx, and tongue, and the role of some nutrients involved in the taste mechanism (e.g., zinc) has not yet been well elucidated [3]. The first molecular encounter with different tastes occurs through membrane proteins—the receptors—located on the surface of the cells, which are responsible for providing the molecular specificity of the gustatory response [2]. This can happen via ion channels that open when they bind to a neurotransmitter (called ionotropic receptors) or via a cascade of reactions induced by proteins (metabotropic receptors) [2]. Salty and sour tastes are identified by ionotropic receptors, whereas the taste of sweet, bitter, or umami are identified by metabotropic receptors [2].

Among other factors associated with dietary changes in cancer survivors (especially those that affect the perception of taste) is the characteristic chronic inflammation that presents with cancer and its impact [4]. There is a release of inflammatory markers via blood circulation into areas of the brain involved in the mechanism of

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taste recognition. Although changes in taste identification are quite common during chemotherapy, they are poorly investigated in clinical practice [5].

In antineoplastic therapy, several drugs have been found to result in taste alterations. Oxaliplatin, for example, is cited in the literature as causing many taste alterations compared with other antineoplastic regimens [6]. Several studies have described changes in taste as a result of chemotherapy, which is characteristically known to influence the results of these changes [5,7,8]. Further, new studies have also pointed to the disease of cancer itself as responsible for taste alterations [4,9].

Among the existing studies on the types of alterations in taste perception in patients receiving cisplatin, some are descriptive and have reported testimonials about patients' observations regarding taste changes [6]. In another study involving a taste test, IJpma et al. [10] found variations in relation to the increase of the perception threshold for salty taste. However, the description of these mechanisms still needs to be improved.

The aim of the study was to evaluate changes in the perception of tastes by participants in platinum derivative treatments and whether these changes involve the mechanisms of recognition of taste receptors.

Materials and methods

The present work was a case control study, submitted to the Research Ethics Committee, approved with identification number 1 409 481. The sample was defined for convenience at the chemotherapy center of a general hospital, with data collection performed for 18 mo, according to the following inclusion criteria: patients under a chemotherapy (QTx) protocol with carboplatin, cisplatin, and oxaliplatin without associated radiotherapy; older than 18 y; of both sexes; non-smokers; and with the absence of oral lesions. The control group (CG) consisted of healthy individuals of both sexes, older than 18 y, who were non-smokers and did not have oral lesions. All the individuals in the CG were companions of the patients.

The participants in the study group (SG) were evaluated at two times: T0, before starting QTx, and again at T1, after two QTx cycles. Contact with the participants was by telephone, and data collection took place at the Clinical Research Unit of the hospital.

The taste tests took place using taste strips (Burghart, Wedel, Germany) that were already validated for this purpose [11]. For the experiment, the presentation of the taste strips was from the lowest concentrations to the largest, with randomly assigned tastes [11]. To classify normogeusia, or the absence of alteration in the perception of tastes, the score was equal to or greater than 08 points, corresponding to the 10th percentile of our sample. Hypogeusia was classified with a score less than 07 points [11].

Analyses were made regarding each taste; the different tastes were grouped by types of receptors—that is, ionotropic (salty and sour) or metabotropic (sweet and bitter)—and separated by the ease of recognition (i.e., sweet and salty and sour and bitter tastes). The aim in classifying taste through receptors was to evaluate which mechanism involved in taste recognition is affected by QTx. The aim in classifying taste based on the ease of recognition was to evaluate whether the scores of the most culturally recognizable tastes differ from the scores of less recognizable tastes to determine whether this recognition influences taste assessment.

To evaluate umami taste, food was offered because umami is not available in taste strips. Cream cheese was chosen because it is a food that is easy to chew and digest and is generally well received by individuals. It was offered on a pita bread in two different ways in a random order: one with no monosodium glutamate (without MSG) and another with an addition of 5% MSG (while still respecting the levels of safe MSG intake). The participants, after tasting the aforementioned products, evaluated their characteristics following a 5-point Likert-type hedonic scale (−1: I hated, −1: I did not like, 0: Indifferent, +1: I liked, +2: I loved), in which the flavor was evaluated.

Two 24-h recalls were collected at both times of the study to assess changes in eating patterns and identify variations in consumption of a zinc, a mineral that has a role in identifying taste. Dietary analysis was performed in software for calculations of nutritional composition of macronutrients and zinc (Dietbox), and the reported values were analyzed by the Multiple Source Method program [12]. To meet the changes made in feeding during treatment, we asked the participants which were and what strategies used to improve it. At both tested times, the participants were weighed and measured for body mass index (BMI) evaluation and classified according to age group [13]. To indicate their functionality, dynamometry was performed using the Saehan hydraulic dynamometer, following the standardized assessment protocol for this goal [14]. Fatigue was also evaluated through a pictographic instrument validated especially for cancer patients [15]. Through two sequences of figures, participants answered how fatigued they felt in the last week and how much it affected their activities [15].

Statistical analysis was performed by the SPSS program with analysis of variance and mixed model of repeated measures and with a significance level of $P \leq 0.05$.

Results

Thirty patients meeting the criteria participated in the study. A total of 4 refused the invitation, 5 completed only the first part of the study, and 21 completed the two interviews. The majority were diagnosed with a tumor of the digestive tract (71.4%) and 40% with metastatic disease. Approximately half (52%) of the group were women. The control group was collected mainly from the patients' companions and was composed of 22 participants, with approximately 63% being women. The characteristics of the sample are shown in Table 1.

For the characterization of nutritional and functional conditions, the variables used were BMI, dynamometry, and fatigue pictogram. There was a significant difference in the dynamometry between groups in addition to the impact caused by fatigue, evaluated by the same instrument. Between the two tested times, we identified a significant difference for this same variable. The results are described in Table 2.

The gustatory changes measured by the intensity scores identified five subjects with hypogeusia in the T0 group and two subjects in the SG. In T1 only one participant presented with hypogeusia, and for that the 10th percentile was considered as the cutoff point for hypogeusia (total hits <7). The results of this evaluation are shown in Table 3.

Table 1
Sociodemographic characteristics of the sample

	SG (n = 21)	CG (n = 22)
Sex		
Female	n = 11(52%)	n = 14 (63%)
Male	n = 10 (48%)	n = 8 (37%)
Age (average)	56, 28 (SD ± 9, 9)	43, 04 (SD± 13, 9)
Years of study		
11 (or more)	1 (5%)	11 (50%)
7–10	8 (40%)	5 (22, 7%)
4–6	12 (55%)	6 (27, 2%)
Occupation		
Working	14 (65%)	19 (86, 3%)
Retired patient	5 (25%)	3 (13, 6%)
Unemployed	2 (10%)	0
Tumor location		
Digestive tube	15 (71, 4%)	—
Others*	6 (28, 5%)	—
Prognostic		
Metastasis	8 (40%)	—
Metastasis absent	12 (60%)	—

CG, control group; SD, standard deviation, ***; SG, study group.
*Others = lung and thymus.

Table 2
Comparison of body mass index (BMI), dynamometry, and fatigue pictogram between the control and study groups

	T0		T1		P	
	CG	SG	CG	SG	T0 × T1	CG × SG
BMI (kg/m^2)	26.9	27.2	26.8	26.5	0.008	0.99
handgrip (kg)	33.5	22, 6	31.5	21.09	0.009	0.04
Pictogram* (0–5)	2.4	2, 2	2.18	2.5	0.98	0.75
Impact (0–5)	1.7	2.9	1.5	2.4	0.006	0.003

BMI, body mass index; CG, control group; QTx, chemotherapy; SG; study group; T0, first evaluation (before QTx); T1, second evaluation (after two cycles of QTx)
*Fatigue Pictogram (evaluation fatigue 0–5), and impact of fatigue (fatigue influence on daily activities 0–5).

Table 3
Description of strategies used by patients to deal with changes in taste perception

Categories	Strategies adopted after chemotherapy
Dietary strategies	
	Avoid pepper
	Increase the use of salt
	Decrease the use of salt
	Begin consumption of dehydrated herbs and industrialized seasonings
	Avoid foods of "difficult digestion"
	Replace dinner with soup
	Replace cow's milk with soy or tea
	Start using teas
	Eat only fresh food
	Start using a nutritional supplement (on your own)
	Support network
	Ask a family member to prepare food for the patient

Table 4
Description of taste scores (sweet, sour, salty and bitter) between SG and CG at both tested times (T0 and T1)

	T0		T1		*P*	
	CG	SG	CG	SG	T0 × T1	CG × SG
Sweet (0–4)	2.95	2.80	3.20	2.80	0.35	0.28
Sour (0–4)	2.72	2.20	2.60	2.30	0.86	0.05*
Salty (0–4)	3.18	1.70	3.00	2.90	0.69	0.001*
Bitter (0–4)	3.00	2.76	3.20	2.76	0.42	0.31
Total (0–16)	11.60	12.00	11.80	12.50	0.38	0.56

CG, control group; QTx, chemotherapy; SG; study group; T0, first evaluation (before QTx); T1, second evaluation (after two cycles of QTx)
*significant difference p> 0.05

Next an analysis was done by grouping the tastes by receptors: ionotropic (salty and sour) and metabotropic (sweet and bitter). The difficulty of recognizing tastes depending on aspects of learning and culture that are involved was considered, and thus we created a category with better known tastes (salty + sweet) and less known (sour + bitter) for comparisons. For the evaluation of the umami taste in the food tasting, in the GC we identified a preference for the product without GSM, without significant difference but with a strong tendency between the groups. The results of these observations are described in Table 4.

There was a significant difference between the average of the ionotropic and metabotropic receptors between the groups, with the CG being larger than the SG, indicating a difference in the identification of salty and sour tastes between the groups.

Among the two tested times, there was a strong trend toward a difference ($P = 0.058$) among the metabotropic receptors, with a significantly higher average in the CG, suggesting that the disease and its treatment plays a relevant role in the adequate identification of these tastes (sweet + bitter).

There was a significant difference between the groups with the CG presenting the highest average for the sweet + salty category, represented by the best-known tastes. There is a strong trend ($P = 0.051$) between the times, with the larger CG average, suggesting that bitter and sour tastes are less well recognized.

Regarding food intake, the data obtained in the 24-h recall were calculated for macronutrient and zinc analysis. The mean energy density (kcal/kg/d) of the CG was 25.3 at T0 and 23.2 at T1, and for the SG, 24.3 and 24.4 at times 0 and 1, respectively; and these values did not present any significant difference. The data referring to dietary analysis are described in Table 5.

The strategies mentioned to improve food intake are presented in Table 6.

Table 5
Comparison of ionotropic and metabotropic receptors, tastes more and less recognized, and food with and without MSG, between the CG and SG at the two tested times

	T0		T1		*P*	
	CG	SG	CG	SG	T1 × T0	CG × SG
Ionotropic (0–8)	5.9	3.9	5.6	4.3	0.874	0.02
Metabotropic (0–8)	5.95	5.5	6.4	5.5	0.058	0.003
S + S (0–8)	6.13	4.5	6.22	4.8	0.051	0.02
B + S (0–8)	5.7	5.00	5.9	5.09	0.11	0.14
No MSG	1.18	0.952	1.22	0.80	0.397	0.446
MSG	0.95	1.14	1.00	1.23	0.436	0.058*

B + S, bitter + sour; CG, control group; MSG, monosodium glutamate; QTx, chemotherapy; SG; study group; S + S, sweet + salty; T0, first evaluation (before QTx); T1, second evaluation (after two cycles of QTx).

Table 6
Density of macronutrients and zinc of the control and study groups at the two tested times

	T0		T1		*P*	
	CG	SG	CG	SG	T0 × T1	CG × SG
Energy (kcal/kg)	25.3	24.3	23.2	24.9	0.52	0.44
Protein (g/kg)	1.16	1.11	1.14	1.21	0.70	0.95
Lipid (g/kg)	0.76	0.86	0.78	0.98	0.36	0.20
Zinc (mg/kg)	0.15	0.13	0.12	0.14	0.57	0.92

CG, control group; QTx, chemotherapy; SG; study group; T0, first evaluation (before QTx); T1, second evaluation (after two cycles of QTx).

Discussion

The results of the taste strip tests indicated a significant difference for the salty and sour tastes between the groups. This result was confirmed in the comparison of ionotropic receptors, suggesting that the physiological changes caused by the disease bring about a compromise in the identification of these tastes. The sweet and bitter tastes, however, did not present any significant differences between the tested times and groups when evaluated individually. However, in the analyses of the groupings of these tastes characterizing the metabotropic receptors, there was a strong tendency toward a significant difference between the tested times and the groups, suggesting an effect of the disease and its treatment with derivatives of platina on these receptors [4].

Recently some papers have explored the contribution of cancer to the changing perception of tastes [9]. In work performed with sprays of taste solutions, Schalk et al. [9] compared groups of cancer patients with participants with non-oncologic chronic inflammatory diseases but who had altered inflammatory markers and concluded that there was a disturbance in the identification of the tastes in both groups, suggesting that this alteration must be due to the characteristic systemic inflammation in the groups studied. In this study, serum levels elevated of C-reactive protein marker were identified, which may indicate the role of inflammation in the interference of taste recognition mechanisms.

Sweet has been described as a dominant taste, even when added in substances with the three other tastes, probably because a larger number of taste buds are related to its identification in the oral cavity. This fact may explain the metabotropic receptor preservation characteristic identified in this study, which, probably by the largest number, may have preserved their identification mechanism for a longer time. We emphasize that the T1 assessment was after two cycles of chemotherapy with platinum derivatives and possibly a change that accentuates with the progress of the treatment. Regarding umami taste, we found a strong tendency for difference in the groups, with a larger average found in the SG,

without identifying a significant difference between the two tested times. Interpreting age, we found averages to be higher in those older than 50 y; therefore, these findings appear to be reinforced by the higher mean age of the SG. There are studies in the literature involving the use of MSG in the elderly, indicating that glutamate may contribute to enhance the taste of foods, even without an evident repercussion on nutritional status [16,17]. Another Brazilian study investigating the threshold of MSG perception in children undergoing treatment for leukemia in Brazil did not find significant differences between this group and healthy children [18].

Considering cultural and cognitive aspects, we found a significant difference between the groups and a strong tendency for the times the most well-known flavors were grouped in the same category. There are data in the literature that indicate that in Western countries, 40% of diet energy comes from sweet foods, 40% from salty, about 10% from sour, and less than 10% from bitter [19]. These data indicate that typically there is little contact with bitter and sour tastes and that this could exert an influence on recognition and learning during taste tests [20]. Köster et al. [20] found that familiarity is developed with exposure to flavors and similarity between their consumption is very common in Western diets as well.

Energy and protein intake between groups and times were similar. The latest recommendation by the European Society of Nutrition and Metabolism is 25 to 30 kcal/kg/d, with a protein supply of 1.2 to 1.5 g/kg/d; and the findings of this study are close enough to this recommendation and have not changed over time [21]. Other studies with cancer patients did not present zinc deficiency before treatment, nor during chemotherapies [22,23]. Study conducted at this same institution with colon cancer patients did not find zinc deficiency, and those participants had a mean of zinc consumption similar to that found in the present study [24].

There was variation among the tested times for BMI, dynamometry, and impact on daily activities associated with fatigue, suggesting that the drugs contributed to impairment of nutritional status and functionality. Among the groups, we identified a difference in dynamometry and its impact on daily activities associated with fatigue, corroborating the fact that since receiving a diagnosis, patients face loss in functional lean mass, and as a consequence they had limitations in their daily activities [14,25]. These observations reinforce data from a study in Brazil, where more than half of the patients diagnosed with cancer presented with malnutrition throughout the treatment, compromising their prognosis [26]. In another study performed at this institution, dynamometry in patients with hepatocarcinoma treated with Sorafenib at the beginning of follow-up was approximately 23 kg, a value close to that found in this study [26]. In the literature to date, little is described about the fatigue associated with platinum derivatives. This effect is more commonly reported in drugs such as doxorubicin and sorafenib, suggesting that this a point to be explored [27].

Limitations of this study include the difficulty in having a complete instrument to test the umami taste, the reduced sample size, not evaluating olfactory changes, and having no dose serum levels of zinc. Another key point is that these taste strips are used in taste tests worldwide and were first used in Brazil, but since being validated in other countries, like Austria, variations of the culture and eating habits may have, in part, contributed to the performance of the instrument [28]. For future studies, considering the interaction of flavor and inflammatory markers at diagnosis would be interesting and enlightening regarding taste alterations.

Conclusions

The findings of this study indicated that patients receiving platinum derivatives have less recognition of salty and sour tastes related to ionotropic receptors; such alteration begins before the beginning of the treatment, indicating a strong association with the physiological alterations of the cancer. Concerning metabotropic receptors, there seems to be preservation for a period of the treatment. Regarding the umami flavor, there is a strong tendency for it to be more exploited and more preferred in the elderly.

The studied drugs seem to influence nutritional status, functionality, and the commitment to perform daily activities.

It is necessary to think about nutritional interventions considering this scenario because it comes up against a series of drawbacks that can compromise food consumption and consequently the clinical outcome of the patient. Nutritional management from the diagnosis should take into account these characteristics, mainly the alterations of ionotropic receptors and their impact on the dietary treatment, so as to contribute toward and perhaps influence the survival of the cancer patient.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2019.06.001.

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