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REVIEW ARTICLE

Dysgeusia in cancer patients undergoing radiotherapy: etiology, diagnosis and therapy

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Abstract:

Introduction: The diagnosis of cancer can provoke innumerable changes in the life of cancer patients, caused by the illness and the methods of treatment. Dysgeusia is a common complication, which directly affects the nutritional status causing loss of appetite and decreased intake. **Aim:** The present paper presents a review of the etiology, diagnosis, and treatment of this oral complication. **Material and methods:** The present literature review selected articles based on the titles that addressed dysgeusia in cancer patients, as well as the etiology, diagnosis and treatment. After previous analysis, we included 31 relevant articles on the proposed theme. **Results:** Dysgeusia can be a symptom or a common consequence of several causes. Radiation therapy may lead to dysgeusia, altering the structure of the pores of the palate or causing a thinning of the epithelium of the papilla. The exact mechanism of dysgeusia in cancer patients is not well elucidated. The diagnosis of dysgeusia can be obtained through objective and subjective methods. The objective methods used are chemical gustometria and electrogustometria. The subjective analysis can be performed through questionnaires where patients report if they noticed changes in taste in the foods consumed daily. Various types of treatments are being used to improve taste disorders, such as zinc supplementation, alpha-lipoic acid (ALA), ginkgo biloba, pilocarpine, transcranial magnetic stimulation, and acupuncture. **Final considerations:** The studies are still inconclusive regarding the etiology of the disease and the treatment methods that reduce the impact of dysgeusia on the life of cancer patients.

Keywords: dysgeusia; head and neck cancer; antineoplastic agent; radiotherapy.

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1. INTRODUCTION

The discovery of cancer generates several changes in the patient's life. In addition to the modifications caused directly by the disease, the methods used for treatment, such as chemotherapy (CT), radiotherapy (RT), and surgery, also induce changes that affect the individual's quality of life[1]. The effectiveness of cancer treatment has improved in recent decades, but undesirable side effects, especially in the head and neck region, are still common[2]. This is a complex area, composed of many different structures that respond differently to radiation. Tissues that rapidly proliferate show acute reactions (initial effects) to RT. The oral cavity is an area that presents acute responses, a result mitotic epithelial cells´ death, which has a short cycle. These reactions include changes such as mucositis, xerostomia, dysphagia, and palate disorders. Reduction in taste sensitivity (hypogeusia), absence of taste sensation (ageusia), or qualitative distortion of the normal taste sensation (dysgeusia) are also common. Other known taste disorders are phantogeusia (distortion in the taste without external stimulus) and parageusia (distortion to a specific stimulus)[3,4,5,6].

Despite the various terms (hypogeusia, ageusia, parageusia, and phantogeusia), the most commonly used term as the general definition for any alteration in the normal taste is dysgeusia[4].

Dysgeusia can lead to nutritional disorders, weight loss, malnutrition, and impaired immunity due to the possible reduction in food intake, altering quantitatively and qualitatively the patient's diet[1] and leading to possible food aversion, distorted odors, and loss of appetite (pleasure in the act of eating) and the inability to identify degrees of harmfulness from food unfit for consumption[7]. It is considered a disease that, depending on the affected level of the patient, may go unnoticed. Increased intake of salt and sugar is common, enough to compensate for loss of taste[4].

Dysgeusia is frequent in cancer patients, affecting approximately 46–77% of individuals, even though it is not often perceived, and it directly affects their lives[8]. The present study brings a current approach to the subject, presenting the etiology of the disease, methods of diagnosis, and therapy.

2. MATERIAL AND METHODS

The present study is a narrative review of literature based on the research of articles conducted in the PubMed and LILACS databases from June 2017 to December 2018, using the cross-referencing of the following descriptors in DeCs/MeSH in English and Portuguese: "dysgeusia" and "disgeusia," "head and neck cancer" and "head and neck neoplasias," "chemoterapy" and "quimioterapia," "radiotherapy" and "radioterapia."

The selection of the articles was based on the titles that addressed dysgeusia in patients with cancer, as well as the etiology of the disease, diagnostic methods, and the general aspects of treatment.

After a previous analysis, 31 relevant articles on the theme proposed for the present narrative review of the literature were included.

3. ETIOLOGY OF DYSGEUSIA

Humans can perceive over a hundred different flavors mediated by the palate. Only five of them are considered "primary" - sweet, salty, sour, bitter, and umami - and can be perceived throughout the lingual region[1,9]. The tongue, soft palate, pharynx, larynx, epiglottis, uvula, and the first third of the esophagus has taste receptor cells that are found in the taste buttons of the papillae[10].

Four morphological types of papillae are found in the oral cavity: fungiform, foliate, circumvallate, and filiform. The latter is the only one that has no taste buds, so it has no function in the perception of flavors. The papillae are bathed by saliva, and the total or partial loss of this secretion can cause palate disorders[1,10].

The taste buttons are composed of approximately 50–150 flavor receptor cells, distributed over different taste papillae. The circumvallate papillae are found on the back of the tongue and have thousands of taste buds. The foliate papillae, containing hundreds of taste buds, are found in the posterior tongue border. The fungiform papillae are located in the anterior part of the tongue, which, when compared to the others, have a smaller number of taste buds[11].

Taste cells have a brief life cicle, approximately 10 days, and are constantly replaced by mitotic division of surrounding epithelial cells. They are organized into four types: basal, dark, clear, and intermediate. Basal cells are considered germ cells. It is believed that these cells give rise to the dark ones, which mature and become clear cells. Finally, they become intermediates and die. Clear cells are responsible for sensory perception and expression of taste receptors. The dark ones are characterized as "support cells" for the others, and intermediates are referred to as "presynaptic cells"[1,9,10,12].

The taste cells project to their surface microvilli, that forms a "gustatory pore," whereby each taste cell forms a site of interaction with the flavors.[11]. Wrapped in the cells are the gustatory nerve fibers, that are stimulated by gustatory receptor cells. The nerve endings of these nerve fibers are excited in response to gustatory stimuli in the oral cavity[9,12]. Thus, the receptor cells of the palate are the only epithelial cells of the human body that have the capacity to generate action potentials and use neurotransmitters, which directly transmit gustatory sensations to the nerve fibers[13].

Some nerves are responsible for the transmission of taste to the brain: facial, glossopharyngeal, and vagus nerves. The facial nerve (cranial nerve VII) is responsible for the gustatory impulses coming from the anterior two-thirds of the tongue. It has a motor and sensory gustatory root and performs this function in two ways: through the tympanum branch of the facial nerve and through the superficial nerve. Stimuli from the posterior part of the tongue and posterior regions of the mouth are transmitted through the glossopharyngeal nerve (cranial nerve IX). The vagus nerve (cranial nerve X) transmits signals from the base of the tongue and other parts of the pharyngeal region[1,9].

Dysgeusia can be a symptom or a common consequence to several causes. Among them are oral and perioral infections, drug use, dental procedures, age, nutritional factors (B12 and zinc deficiency), multiple sclerosis, amyotrophic lateral sclerosis (ALS), oral cavity tumors, and CT and RT for head and neck cancer[10].

Taste change is a premature response to the effects of head and neck RT. Most patients have partial or total loss of taste during treatment, and it is strongly related to hyposalivation, another acute response to RT. The reduction in salivary flow decreases the transport and solubilization of gustatory stimuli, causing inability to perceive flavors[3]. Cancer treatment can also affect neural activities and receptor cells, thus modifying the afferent taste pathways. Radiation therapy may lead to dysgeusia, which alters the structure of the pores of the palate, with consequent thinning of the epithelium of the papilla[14]. Hypotheses have been raised to explain the impairment of the palate induced by irradiation. These include inflammation of the afferent nerves that supply the taste buds, direct damage to the differentiation of taste cells, and, finally, eradication of proliferation progenitors, which prevents the renewal of the taste cells with short cell cycle[15]. However, although there are hypotheses, the exact mechanism of dysgeusia in cancer patients is not, in fact, well elucidated[1].

Dysgeusia can be found in approximately 66.5% of patients who receive RT in the head and neck region and 76.0% of patients who undergo chemoradiotherapy in the same region. This condition also presents as a late effect, where about 15% of the patients continue with taste alteration even after the RT is finished[16].

4. DIAGNOSIS OF DYSGEUSIA

The diagnosis of dysgeusia can be obtained by objective and subjective methods. The objective methods used are chemical gustometry and electrogustometry (EGM). The first can be performed through paper strips or aqueous solutions. The substances are offered to the patients in different concentrations to allow the qualitative and quantitative analysis of the flavors, evaluating the type of loss of sensitivity and its intensity[5]. The substances commonly used are sucrose, for the perception of sweet taste; sodium chloride, for salty taste; citric acid, for sour taste, and quinine sulfate or caffeine for bitter taste[17]. For the umami flavor, the combination of monosodium glutamate and inosine monophosphate-3 is commonly used[1]. EGM is the use of electrical stimulation on the gustatory receivers. It is able to evaluate only the sour taste, so it is not considered a qualitative test. Moreover, it presents a low correlation between the perception of the electrically and chemically induced palates (e.g., chemical stimulants present in foods) and causes tingling sensations, vibrations, and small shocks, thus having limited clinical use. The test with the taste strips and EGM test can evaluate the change in specific sites of the oral cavity and can be useful tools to understand the physiology of dysgeusia[6,18].

The subjective analysis can be performed through questionnaires where patients report if they noticed changes in taste in the foods consumed daily. To complement the subjective assessment, the National Cancer Institute's Common Criteria of Toxicity (NCI) can be used. The severity of the taste dysfunction can be graded from 0 to 2, with grade 0 for no change, 1 for slight alteration, and grade 2 for pronounced alteration[19].

RT or chemoradiotherapy in patients with head and neck cancer is considered one of the major causes of dysgeusia. In a study conducted by Baharvand et al.[5], 22 patients with head and neck cancer were followed up during cancer treatment. The researchers analyzed patients before and after three weeks of RT and used chemical gustometry as the test for the detection of dysgeusia. All patients presented dysgeusia, and 72.2% had a total loss of taste.

McLaughlin[13], conducted a study with the objective of observing the prevalence of palate dysfunction in 92 patients with at least three months of termination of the RT for head and neck cancer. The taste test (gustometry) was used to detect abnormalities in the capacity and intensity of tasting of four basic flavors (sweet, salty, sour, and bitter). Three different concentrations of test solutions were used as low, medium, and high. A total of 92.4% (n = 85) of patients presented with dysgeusia.

Pavlidis et al.[20], analyzed 20 patients with head and neck neoplasia to evaluate the gustatory function and accompanying changes in morphology and vascularization of the tongue mucosa. The patients were submitted to EGM in six areas of the mouth region, contact endoscopy, and subjective questionnaire. For those who received RT, tests were performed before treatment, three weeks after onset, and at the end of the treatment. After 3 weeks, all patients presented high EGM thresholds, that is, changes in taste perception. Some have reported phantogeusia and ageusia. In the last measurement, in all 6 areas, complete ageusia was observed. Patients reported an inability to recognize any stimulus. All patients presented significant changes in the vascularization of the tongue's apex.

Another study analyzed 51 patients with head and neck cancer who underwent RT. The loss of 5 flavors (sweet, salty, bitter, sour, and umami) was evaluated. The filter-paper disk method was used, with five different concentrations of the test solutions. All patients presented a reduction in sensitivity for all flavors during the RT process[21].

5. TREATMENT

Dysgeusia is a common complaint in approximately 70% of patients who undergo head and neck RT. The onset is common from the second or third week of treatment and may last for weeks or even months. It is a normally reversible symptom[22]. However, during its course, it contributes substantially to inappetence (lack of appetite), reduction in dietary intake, weight loss, and consequent negative impact on the quality of life of these patients[15].

Various types of treatments are being used to improve palate disorders. Zinc supplementation has been suggested as one of the forms of treatment for dysgeusia, showing functionality in the process of regeneration of the taste buds that were injured. It is known that deficiency of this nutrient can lead to hypogeusia. The taste buds depend on calcium to function properly. The efficacy of zinc supplementation is still somewhat controversial in studies with a low population sample and because of the different causes of dysgeusia[23,24].

A study was carried out with 169 patients who were treating head and neck cancer, submitted to RT, which presented with palate disorders. Treatment with zinc sulfate was performed throughout the RT period and one month after its completion. The aim of the study was to determine whether supplementation delays the development of dysgeusia in these patients. The zinc sulfate group did not show a significant decrease in the incidence of palate changes compared to the placebo group[25].

Photobiomodulation therapy may also be indicated for the treatment and prevention of dysgeusia and other complications of RT[16,26]. In a case report of a patient with malignant head and neck neoplasia and taste disorders, the intraoral application of a diode laser with a wavelength of 980 nm was used in 10 points in the dorsal and lateral region of the tongue with energy density of 3 J/cm^2 and duration of 12 s at each point to evaluate the impact of this therapy on dysgeusia. The sessions were repeated 3 times for one week, with 48 h between each session. It was observed that photobiomodulation was effective in restoring the palate, because the degree of perceived taste was significantly higher on the last day compared to the first day of evaluation. The degrees of dysgeusia were evaluated according to the taste test proposed by the International Organization for Standardization. Five basic taste test solutions (sweet, salty, sour, bitter, and umami) were used[16].

Among other treatment methods that were tested for the different causes of dysgeusia are alpha-lipoic acid (ALA) supplementation, *Ginkgo biloba* use, pilocarpine, transcranial magnetic stimulation, and acupuncture. However, further research should be performed to confirm efficacy of these therapeutic agents in the treatment of dysgeusia[23].

Constant nutritional monitoring is essential for cancer patients and those who are still diagnosed with dysgeusia, where, under these conditions, malnutrition is a frequent consequence. The maintenance and/or improvement of the nutritional status of the patient is associated with greater effectiveness of the treatment and improvement of the quality of life. Lack of nutritional support may lead to reduced treatment control, due to the increased risk of the interruption of the treatment and infections[6,27,28].

One study pointed out that patients had late effects after the treatment for head and neck cancer. These late effects directly affected the quality of life in relation to the habit of eating. Patients reported that they did not regain full taste perception even after 3 years of treatment conclusion[29].

During the onset of the symptoms, preparations with a more intense flavor are recommended, in order to minimize the effect caused by changes in taste. Since dysgeusia is closely associated with xerostomia, intake of foods that promote salivation, such as citric fruits (in the absence of mucositis), due to the presence of ascorbic and citric acid, or other fruits such as apples and pear, which contain malic acid, in addition to chewing gum, is also suggested[30,31].

6. FINAL CONSIDERATIONS

Dysgeusia, or distortion of taste, is a common consequence in patients with cancer, which may appear as a consequence of disease or may be associated with treatment. It is common in patients with head and neck tumors, especially those submitted to RT.

Commonly impacting on the patient's quality of life, dysgeusia can lead to reduced food intake, with changes in nutritional status, which decreases the patient's response to antineoplastic treatment and increases morbidity and mortality.

The studies are still inconclusive on the etiology of the disease and the treatment methods that reduce the impact of dysgeusia on the life of cancer patients. Further research is needed to understand the nature, diagnosis, and severity of this disease and effective treatment methods.

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