JGG JGG 2020;68:77-84
10.36150/2499-6564-484

Review

Swallowing and secretory senescence

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Glandular senescence is a pathophysiological process that can alter the swallowing process in all its stages. The production of saliva in the elderly changes both qualitatively and quantitatively; qualitative alterations are more objective than quantitative alterations, whose measurement methods are still under discussion. In the elderly, xerostomia is not always related to hyposalivation, and hyposalivation is not strictly related to glandular senescence. In these patients, a reduced functional reserve can turn a physiological presbyphagia to a pathological dysphagia. The analysis and recognition of the signs and symptoms of this process require a multidisciplinary approach and the implementation of appropriate therapies.

Key words: presbyphagia, xerostomia, elderly, swallowing function, dysphagia

INTRODUCTION

The well-being of an individual depends on innumerable variables that cannot be catalogued in order of importance. Among these, we must surely include the normal salivary function whose exact physiological features are difficult to define. It is well known and intuitive how anything that alters salivation in a hyper- or hypo-productive sense leads to a management problem at the swallowing level that can quickly cause a deterioration of the life quality. In this paper, we will try to understand the correlation between the production of saliva and the swallowing function by identifying the causal link between the onset of physiological presbyphagia and any subsequent dysphagia. We will start by a brief and preliminary consideration of the anatomical and physiological aspects that characterize the swallowing function.

SWALLOWING PATHOPHYSIOLOGY

Swallowing is a highly complex process in which voluntary and involuntary muscles are involved. The cranial nerves V, VII, IX, X and XII innervate about 40 muscles bilaterally, represented by the muscles of the oral cavity, pharynx, larynx and esophagus. The food is chewed, transformed into bolus and transported to the pharynx from the tongue, while the liquids are first retained in the oral cavity and then transferred to the pharynx. The muscles involved in these phases are coordinated by the swallowing centers located in the brain stem which, in turn, receive sensitive information from the cranial nerves and input from the cortical centers. Therefore, the swallowing process is composed of voluntary and involuntary phases [1].
Among the various existing schemes, we have chosen the one that breaks

Received: April 14, 2020
Accepted: June 3, 2020

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Conflict of interest
The Authors declare no conflict of interest

How to cite this article: Caliceti U, Lo Russo MG, Mattucci G, et al. Swallowing and secretory senescence. Journal of Gerontology and Geriatrics 2020;68:77-84. https://doi.org/10.36150/2499-6564-484

swallowing into 6 phases: the anticipatory phase, the preparatory oral phase, the oral transit phase, the oropharyngeal phase, the pharyngeal phase, and the esophageal phase [2].

Since salivation and chewing play a decisive role in the preparation of the bolus, which takes place in the oral phase, we believe that we should focus mainly on the oral phases and the subsequent oropharyngeal phase.

The oral phase is mainly a voluntary process that the individual can start at any time, and consists of two different times that are carried out in succession: first, the preparation of the bolus, secondly, its propulsion towards the pharynx [3].

The treatment of the complex physiology of swallowing is beyond the scope of our paper, so please refer to an in-depth examination on specific texts.

THE ROLE OF SALIVA IN SWALLOWING

Saliva is a complex biological fluid naturally secreted by the salivary glands in the oral cavity [4]. In humans, there are three pairs of major salivary glands (MSGs) that secrete 92-95% of total saliva (parotid, submandibular and sublingual glands) while the minor salivary glands (mSGs) are located in the mucous membranes of the mouth, lips, palate and lingual region, and secrete the remaining saliva [4].

Saliva is produced in basal conditions and upon stimulation, and the daily amount varies from 0.5 to 1.5 L/day. 65% of basal saliva is produced by the submandibular glands, 7% by the sublingual glands, and about 20% by parotid glands; however, upon stimulation, production is mainly ensured by parotid glands (Figs. 1-2) [4].

In addition to the change in quantity, there are also differences in terms of quality of the saliva produced at basal level or under stimulus; the latter is more fluid because it contains less proteins (mucins), which are mainly responsible for the saliva viscosity. Numerous studies demonstrated the difference between the two types of saliva by analyzing their rheological (from "rheology", a science studying the deformation characteristics of solid bodies under the action of external forces and, in particular, the flow of fluids and semi-fluids with reference to their properties and their relationship with the surrounding environment) and tribological properties (from the Greek *tribos*, which means friction, and *logo*, which means study or science, thus literally "the science of friction"). These differences are basically due to the different histology of MSGs, whose acinar cells secrete different glycoproteins.

The objective evaluation of saliva production is based on the measurement of saliva flow in basal conditions [4]. Table I summarizes the physiological characteristics of MSGs [5].

Saliva plays a fundamental role in maintaining oral health, therefore any alteration in its quantity or composition may compromise the integrity of the hard and soft tissues of the mouth, as well as oral and gastrointestinal functions.

The roles saliva plays in the correct performance of the swallowing function are countless. In the anticipation phase, the elicitation of salivation in response to visual or olfactory stimuli or the mere thought of food is of fundamental importance in order to begin the swallowing process in the best possible conditions. Among the main roles played especially in the oral phase, we list:

- *bolus formation.* The saliva joins the food so that the bolus can be smooth, compact and easily glide over the mucous membranes [4];
- *perception of taste sensitivity.* The food components responsible for taste perception are diluted in aqueous suspension in the saliva, allowing the particles to interact with the receptors located on the taste buds [4];

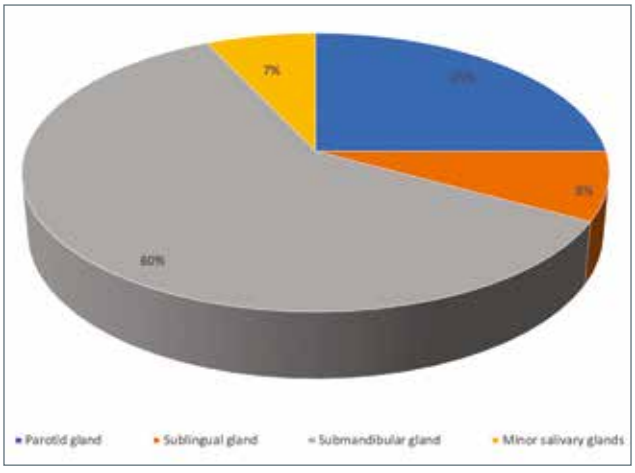

Figure 1. Saliva production at rest.

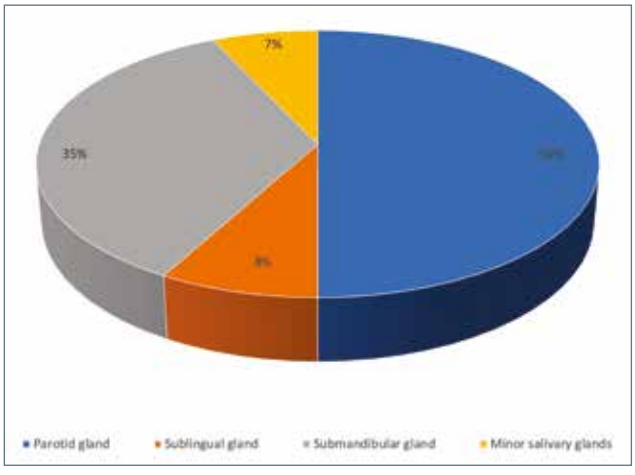

Figure 2. Saliva production upon stimulation.

Table I. Physiological characteristics of MSG (from Petersen et al., 2018, mod.) [5].

	Type of acinar cells	Type of saliva produced
Parotid	Serous	Aqueous, rich in amylase
Submandibular	Mixed, mainly serous	Viscous, rich in mucin
Sublingual	Mixed, mainly mucinous	Viscous, rich in mucin
Minor salivary glands:	Mixed	
• **palatine**	Mucous	Rich in mucin
• **buccal**	Mixed (+mucous)	Rich in mucin
• **labial**	Mixed (+mucous)	Rich in mucin
• **lingual**	Serous	Aqueous, rich in lipase
• **retromolar**	Mucous	Viscous, rich in mucin

- *moisturization of the mucous membranes.* The saliva adheres to the surfaces of the oral cavity maintaining a constant layer of about 30-100 nm thick. The proteins contained in it, in particular mucin, provide the rheological and tribological properties, while the aqueous component guarantees the hydration and lubrication functions [4];
- *immune and antibacterial function* [4]. This is carried out by immunoglobulins, lysozyme, lactoferrin, lactoperoxidase, agglutinin, histatin and cystatin. An impaired saliva production is a cause of oral health impairment, resulting in an increased risk of infections of the oral mucosa and teeth [6];
- *speech articulation.* Slurred speech is a symptom often complained of by geriatric patients, caused by the inability of saliva to maintain the oral cavity adequately and uniformly lubricated [4];
- *cleaning of the oral cavity and its protection.* Thanks to its bicarbonate ions, saliva has a buffering effect against acids present in food or in any endogenous refluxes, potentially harmful to the mucous membranes of the oral cavity and the first airways and digestive tract.

With ageing, there are numerous changes that alter the salivary glands, but literature lacks a clear correlation between ageing and the actual amount of saliva produced. The changes concern various aspects:

- *histological alterations* with an increase in the volume of the ducts, reduction in the volume of the acini and their replacement by fibrovascular tissue [7];
- *neurophysiological alterations*, which cause a decrease in the afferent stimulus with consequent hypostimulation (decrease in gustatory receptors, demyelination of nerve fibres…) [4];
- *vascular alterations* cause glandular hypoperfusion and, consequently, functional decline, hence the slowed tissue repair capacity [4].

Changes in quantity and quality of saliva

Saliva performs its multiple functions thanks to the properties that derive from physical (rheological and tribological properties) and chemical (action of specific components, protein and ionic components) characteristics.

An explanation of the correlation between hyposalivation and dysphagia may derive from a hypothetical reduction in the thickness of the saliva film, with insufficient lubrication during the swallowing phase and consequent increase in bolus resistance during its transfer. Another factor contributing to dysphagia is the persistence of food fragments attached to the mucous membranes, a symptom often complained of by patients with xerostomia [6].

The quantitative alteration of saliva production is measured by sialometry; this measurement is carried out both in basal conditions and under stimulus, and allows to detect the global production of the MSGs but also the selective production of a single gland by means of cannulation of the main duct. However, these methods are difficult to implement in clinical practice and have, therefore, been replaced by less specific but easier examinations, such as sialography, scintigraphy and MRI. Although easier administration tests have been proposed in the past years to measure the production of saliva based on the imbibition of different materials (e.g. modified Schirmer test, Saxon test), to date there are no studies to confirm their effective application in clinical settings.

With regard to qualitative changes in saliva in the elderly, there is evidence that the loss of anions alters the tertiary structure of mucin, which changes from an ordered polymeric form to one characterized by aggregated polymeric residues; this reduces the water retention capacity of mucin and, consequently, alters the quality of lubrication of the oral cavity. This partially explains why elderly patients suffer from xerostomia despite the fact that they have almost stable levels of mucin [6].

The determination of quality alterations in saliva is difficult to perform and standardize due to the difficulty to adopt reference standards and, above all, to apply them in clinical practice.

XEROSTOMIA AND HYPOSALIVATION IN GERIATRIC PATIENTS

Xerostomia is just one of the various factors contributing to dysphagia and is rarely the only one. The main causes are listed in Table II [8].

The term xerostomia defines the subjective sensation of dryness of the oral mucosa due to reduced lubrication. This is not necessarily related to hypofunction of the salivary glands [4].

Instead, hyposalivation is defined as the objective reduction in salivary flow, which is often related to the sensation of xerostomia [6].

In clinical practice, it is advisable to differentiate the two terms as xerostomia is a commonly reported symptom by the elderly, with an estimated prevalence between 12 and 40%, while the objective reduction in salivary flow (hyposalivation) does not seem directly related to ageing although there is a high probability of finding factors contributing to the pathological decrease in salivary flow in the elderly [2].

There are various studies showing that the production of saliva by parotid, submandibular and sublingual glands does not significantly decrease with ageing. However, numerous iatrogenic causes such as drugs, radiotherapy, surgery, as well as various systemic diseases (Sjogren's syndrome, PBC, decompensated DM, depression) are clearly identified as etiological factors for xerostomia. There are more than 700 drugs that can cause xerostomia and, especially under conditions of prolonged combination therapy, they can contribute to cause hyposalivation [9].

It should also be noted that, as in a vicious circle, combination therapy can cause additional oral disorders such as burning mouth syndrome, whose pharmacological treatment (tricyclic antidepressants) is the cause of hyposalivation itself.

Thus, we can say that drugs and comorbidities are the main causes of xerostomia and hyposalivation in the geriatric population [10].

We can add another factor to the above-mentioned, which is often found in the elderly population, that is dehydration, which helps to support the vicious circle resulting in hyposialia and consequent xerostomia.

SWALLOWING AND SENESCENCE: FROM PRESBYPHAGIA TO DYSPHAGIA

Ageing produces changes that cannot be defined as pathological but that affect the swallowing process.

In general, the term "dysphagia" means any swallowing disorder that compromises the safety of the swallowing mechanism (e.g. inhalation) or the efficiency of the swallowing act (e.g. stagnation, increased bolus transit time, incoordination of the phases).

The term "presbyphagia" refers to the physiological deterioration of that complex system of anatomical, neurological and functional variables which, changing inexorably with age, contribute to the progressive deterioration of the quality of the swallowing mechanism in the elderly. Unlike dysphagia, presbyphagia is generally asymptomatic but can evolve, due to the acceleration of the deterioration processes, towards a real "presbyo-dysphagia", that is the appearance of dysphagia in a presbyphagia context.

Weakness of the lingual and other muscles in the oral cavity, as well as decreased sensitivity, can compromise the preparatory and propulsive phases of the bolus. The tongue provides the initial impulse for the bolus to pass through the pharynx; a sensory deficit at this level or incoordination of the pharyngeal muscles can lead to slower transit or stagnation of food in the oropharynx. Weakness of the pharyngeal muscles can also lead to incorrect passage of material into the nasopharynx. Due to age-related neuronal loss, both in the brain and at the nerve endings, there is also a slower closing of the laryngeal vestibule and relaxation of the upper esophageal sphincter. The weakness of the pharyngeal muscles may decrease the opening of the upper esophageal sphincter or cause inadequate bolus propulsion. Finally,

Table II. Xerostomia causes.

Central nervous system	Peripheral nervous system	GLAND
Drugs	Neuropathies (diabetic, degenerative, demyelinating, infectious)	Sjögren's syndrome
Mood (stress, anxiety, depression)	Traumas	Diseases with granulomas (TB, sarcoidosis)
Brain neoplasms	Infiltrating or nerve compressing neoplasms	Collagen diseases
Neurodegenerative diseases	Iatrogenic nerve damage	Graft *vs* host disease
Parkinson's disease		Radiotherapy
Stroke		Primary and secondary gland neoplasms
		Systemic diseases (diabetes, CKD)
		Infectious diseases (HIV, HCV)
		IgG4-related disease

incoordination and muscle weakness may result in failure of the airway protection mechanism [1].
Presbyphagia develops in parallel with the senescence process and the transition from presbyphagia to dysphagia occurs when any pathological condition, overlapping with an already reduced functional reserve such as in the case of an elderly patient, destabilizes the precarious balance which is based on adaptation and compensation strategies [11]. For this reason, presbyphagia cannot be considered as a real pathological state, but it can become so by falling into an acute situation of dysphagia [12].
The prevalence of dysphagia in the elderly population is estimated at around 13% at the age of 65, rising to 16% between 70-79 years of age and 33% in the elderly aged over 80 [11]. These data, in industrialized countries, are expected to increase in the coming years due to the progressive increase in average life expectancy.
Therefore, it is important to point out how presbyphagia is part of those manifestations recognized as "geriatric syndromes", whose foundation is the decrease in the functional reserves of the body following a compromised compensatory capacity [11].

Dysphagia in the context of geriatric syndromes: the concept of "Oral Hypofunction"

In 2016, the Japanese study group of the National Center of Geriatrics and Gerontology introduced a new concept of progressive decline in general function starting with the reduction of oral function. The term "Oral Frailty" was coined to mean the non-specific weakening of the oral cavity functions. This is characterized by defined signs and symptoms such as difficulty in speech articulation, food spillage during mealtime, and an increase in the number of foods posing chewing difficulties.
Oral weakness does not represent a pathological state but expresses a partially deteriorated physiological condition. According to the Authors, this condition can be potentially recovered by taking care of oral hygiene to prevent periodontitis and caries, and by counteracting the deterioration of chewing function with the adoption of appropriate dental prosthesis. Therefore, there is a progressive awareness that the recovery and maintenance of good oral function delays the appearance of conditions that imply care needs, thus affecting the improvement of life expectancy.
Following the concept of "Oral Frailty", the concept of "Oral Hypofunction" has been introduced, understood as the stage of decay in which recovery is still possible by implementing appropriate treatments; in case of further deterioration, the next stage is called "Oral Disfunction" [13].
Oral Hypofunction is defined as the presence of at least 3 of the oral signs or symptoms listed in Table III.
The idea that "Oral Frailty" and "Oral Hypofunction" are two stages of functional decline leading progressively to "Oral Dysfunction" is quite similar to the above-mentioned concept of progressive transition from presbyphagia to presby-dysphagia and dysphagia (Fig. 3).

HOW TO IDENTIFY THE ELDERLY PATIENT AT RISK OF DYSPHAGIA

Signs and symptoms

The most frequently reported symptoms include feeling of pharyngo-laryngeal obstruction in 21%, cough in 10% and itching/throat clearing in 7% of cases. However, one cannot affirm that these symptoms are pathognomonic or predictors of dysphagia as they are frequently found in many other diseases of the pharyngo-esophageal tract [11].
Other symptoms of dysphagia may be weight loss, the need to drink a lot of water, the presence of food debris on the mucous membranes and an increase in the time necessary to eat [2].
Table IV lists the symptoms that should make one suspect dysphagia.
In case of a clinical suspicion of dysphagia, it is necessary to pursue a diagnostic path that first involves an accurate clinical evaluation and, if necessary, the carrying out of instrumental investigations.

Clinical diagnosis

Dysphagia in the elderly population can be detected by the general practitioner through routine clinical checks,

Table III. Signs and symptoms of oral hypofunction (from Minakuchi et al., 2018, mod.) [13].

Clinical signs	Measurements
Poor oral hygiene	The total number of microorganisms (CFU/mL) is $10^{6.5}$ or more
Oral dryness	The measured value obtained by a recommended moisture checker is less than 27.0
Reduced occlusal force	The occlusal force is less than 200 N
Decreased tongue-lip motor function	The number of any counts of/pa/,/ta/or/ka produced per second is less than 6
Decreased tongue pressure	The maximum tongue pressure is less than 30 kPa
Decreased masticatory function	The glucose concentration obtained by chewing gelatin gummies is less than 100 mg/dL
Deterioration of swallowing function	The total score of EAT-10 is 3 or higher

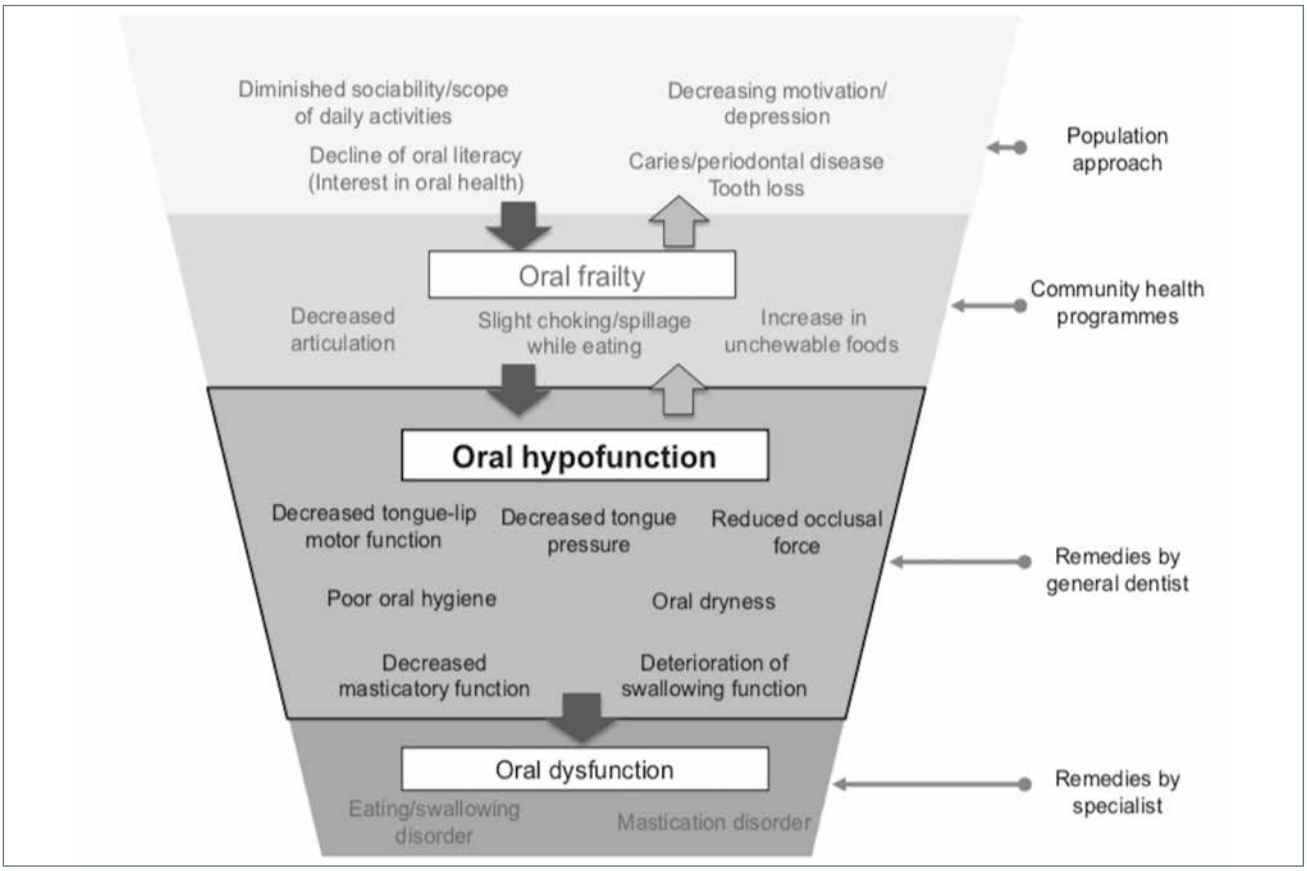

Figure 3. The transition between oral frailty, oral hypofunction and oral dysfunction (from Minakuchi et al., 2018, mod.) [13].

which may be followed by functional evaluation by means of a specific protocol.

Currently, the *Volume Viscosity Swallow Test* (V-VST), the *Sydney Swallowing Questionnaire* (SSQ), and the *Eating Assessment Tool-10* (EAT-10) are the 3 validated protocols available, but the most widely used one, especially in institutionalized patients, is the EAT-10.

The V-VST is more difficult to administer because it requires an adaptation of the protocol according to the patient's response to each swallowed act, although it has a good sensitivity and specificity in diagnosing oropharyngeal dysphagia (94 and 88%, respectively), therefore it is not the first protocol to choose in case of large-scale screening [12].

The EAT-10 investigates the swallowing difficulties encountered by the patient or his/her caregiver with 10 entries by assigning a score from 0 to 4 for each entry (0 = no problem, 4 = serious problem). A final score > 3 suggests that the patient is at high risk of dysphagia. The sensitivity and specificity of this test are 89 and 82%, respectively; this protocol is likely to be administered in the GP surgery both to the patient and the caregiver, or in the waiting room during the wait, and is, therefore, the most suitable one in daily practice [12].

Instrumental diagnosis

If the results of questionnaires or a strong clinical suspicion lead to the diagnosis of presbyphagia and probable dysphagia, it is necessary to complete the diagnostic procedure by means of instrumental investigations that make it possible to better identify the functional defect. These investigations consist in the study of swallowing by videofluoroscopy or fiberoptic endoscopic evaluation [12].

Table IV. Symptoms of dysphagia.

Typical symptoms	Typical and often neglected symptoms	Atypical symptoms
Coughing during meals	Sialorrhea	Weight loss
Voice alteration during meals	Itching	Respiratory alterations during meals
Swallowing pain or discomfort	Lengthening of the time necessary to eat	Bronchial obstruction
Feeling of food bolus	Reduced food intake	Recurring bronchopulmonary infections
Regurgitation of food in the nasopharynx	Discomfort in eating in public	Febrile episodes of undefined origin

Answer each question by ticking the value corresponding to the extent of the symptom. 0= no problem, 4= serious problem

1) The difficulty in swallowing caused me to lose weight.

2) The difficulty in swallowing makes it difficult for me to lunch out

3) I find it difficult to swallow liquids

4) I find it difficult to swallow solid food

5) I have difficulty in swallowing medicines (pills, tablets, capsules)

6) Swallowing causes me pain

7) The difficulty in swallowing reduces my enjoyment of the meal

8) When I swallow, food stops in my throat.

9) When I eat, I cough

10) Swallowing causes me anxiety

Figure 4. EAT-10 (from Belafsky et al., 2008, mod.) [14].

Study of swallowing by videofluoroscopy, or barium meal, is the only imaging examination that allows to investigate all 4 stages of swallowing. This remains the pivotal study in the diagnosis and evaluation of the dysphagia patient and is useful in determining the most suitable rehabilitation strategy and possible therapy [12].

Fiberoptic endoscopic evaluation of swallowing. One of the main advantages of this technique is that it can be performed at the patient's bedside and is, therefore, preferred in hospitalized and bedridden patients [2]. Studies have shown that this evaluation identifies about 1/3 of patients at risk of dysphagia who were found healthy on a normal fiberoptic test [11].

While being of specialist competence (radiologist and ENT specialist), both methods give the possibility to carry out a multidisciplinary evaluation.

DYSPHAGIA TREATMENT IN RELATION TO HYPOSALIVATION

The main objective of any approach, both diagnostic and therapeutic, is to reduce the patient's difficulties and to prevent the onset of complications, considering that elderly patients often have reduced functional reserves, thus the appearance of a minimum damaging element is enough to cause the destabilization of an already precarious balance.

Depending on the primary cause of xerostomia or hyposalivation, there are various therapeutic alternatives:

- suspend or change the drug therapy considered as potentially responsible, carefully evaluating the risk/benefit ratio of each drug;
- recognize and treat the systemic pathologies responsible for hyposialia;
- use substances that promote the production of saliva with lubrication effect, such as toothpastes and mouthwashes, sorbitol and xylitol-based chewing-gums, citric acid tablets;
- use substances that make up for the lack of endogenous saliva. These products belong essentially to three broad categories depending on their composition: (1) biopolymer-based substitutes such as plant mucilage, animal mucin or xanthan gum; (2) substitutes based on salivary enzymes; (3) acid-base substitutes. Products based on Biotene®, a hybrid of plant mucilage biopolymers and

salivary enzymes, have shown effective xerostomia reduction in many patients. However, the function of these products on swallowing quality has not been proven yet [6];
- use food conveyors (e.g. oil, mayonnaise) to facilitate the transport of food and mix its components;
- in patients with etiological risk factors of tissue damage, such as radiotherapy and chemotherapy, it is important to comply with hygiene regulations such as smoking cessation, avoid mucosal irritants such as alcohol and coffee, frequently sip water, avoid dry environments and take care of daily oral hygiene [8].

A study evaluating lingual muscle strengthening exercises to improve dysphagia due to sarcopenia, regardless of age, showed that the perceived effort is greater in patients with xerostomia as well. This result suggests that adequate lubrication of the oral cavity is important to facilitate the swallowing act and decrease related fatigue [6].

The review of the literature shows the difficulty in identifying how a change in saliva quantity and quality determines an increased swallowing effort.

Therefore, it is as logical as important to work on food consistency, a trivial observation which, however, represents the only choice that can be made in the case of dysphagia related to xerostomia and hyposalivation.

CONCLUSIONS

The correlation between swallowing and secretory senescence remains a difficult subject to deal with. The reduction in saliva flow in the elderly certainly has a physiological component, with quality and quantity alterations of the saliva; however, the taking of drugs and the degeneration of the anatomical structures involved in the act of swallowing contribute to this reduction. Hyposalivation and the consequent xerostomia exert a cascade effect on oral physiology and the swallowing quality. Other multiple variables such as the condition of the mucous membranes, muscles and paths involved in the swallowing function contribute to the worsening of the swallowing capacity.

Therefore, a process of progressive deterioration of the already precarious anatomo-functional balance, called presbyphagia, arises in the elderly and can easily precipitate into a pathological state of dysphagia. There are many players involved in the early diagnosis of presbyphagia, to underline how the multidisciplinary approach is mandatory in ensuring a rapid regression of dysphagia to presbyphagia and avoiding repercussions on the health status and life quality of the elderly patient.

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