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## Review article

# Sialometry: aspects of clinical interest

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### ABSTRACT

Whole saliva is a multiglandular secretion complex consisting of gingival fluid, desquamated epithelial cells, microorganisms, products of bacterial metabolism, food debris, leukocytes mucus from the nasal cavity and the pharynx. Saliva has many functions, including tissue repair, tamponage, protection, digestion, taste, antimicrobial action, maintaining tooth integrity and antioxidant defense system. A decrease in salivary flow (hyposalivation) is a common disorder and it is estimated that approximately 20% of the general population have this alteration.

Hyposalivation may be due to diabetes mellitus, hypothyroidism, dehydration, impaired glandular parenchyma by infectious processes, granulomatous diseases or autoimmune and inflammatory conditions (such as Sjögren's syndrome and rheumatoid arthritis), radiotherapy of head and/or neck region, or it may be associated with mood disorders, adverse effects caused by the use of some medications or even be idiopathic. Conventional therapies for the treatment of reduced saliva flow with the use of chemical and gustatory secretagogues are still limited.

However, new alternatives have shown great perspective in the treatment of this disorder. To diagnose a patient as having chronic hyposalivation is a challenge in clinical practice and methods of salivary flow assessment are little known by rheumatologists. The serial evaluation of salivary flow is important for the diagnosis and prognosis of certain oral and systemic conditions. This review addresses some aspects related to the role of saliva, the consequences of hyposalivation and methods of salivary flow rate measurement, useful concepts in the daily practice of rheumatology.

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## Sialometria: aspectos de interesse clínico

### R E S U M O

#### Palavras-chave:

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A saliva total é um complexo de secreções multiglandulares composto de fluido gengival, células epiteliais descamadas, microrganismos, produtos do metabolismo bacteriano, resíduos alimentares, leucócitos, muco da cavidade nasal e da faringe. A saliva possui diversas funções, incluindo reparação tecidual, tamponamento, proteção, digestão, gustação, ação antimicrobiana, manutenção da integridade do dente e sistema de defesa antioxidante. A redução do fluxo salivar (hipossalivação) é um distúrbio comum, e estima-se que cerca de 20% da população geral tenham esta alteração.

A hipossalivação pode ser decorrente de diabetes mellitus, hipotireoidismo, desidratação, comprometimento do parênquima glandular por processos infecciosos, doenças granulomatosas ou condições autoimunes e inflamatórias (como a síndrome de Sjögren e a artrite reumatoide), radioterapia da região cefálica e/ou cervical, bem como pode estar associada a distúrbios do humor, efeitos adversos ocasionados pelo uso de algumas medicações ou, ainda, ser de causa idiopática. As terapias convencionais para o tratamento da redução do fluxo salivar, com o uso de sialogogos gustatórios e químicos, ainda apresentam restrições.

Contudo, novas alternativas têm mostrado grande perspectiva no tratamento deste problema. Diagnosticar um paciente como hipossalivador crônico é um desafio na prática clínica, e os métodos de avaliação do fluxo salivar são pouco conhecidos pelos reumatologistas. A avaliação seriada do fluxo salivar é importante para o correto diagnóstico e prognóstico de determinadas condições bucais e sistêmicas. Esta revisão aborda alguns aspectos relacionados à função da saliva, às consequências da hipossalivação e aos métodos de medição da taxa de fluxo salivar, conceitos úteis na prática diária do reumatologista.

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## Introduction

Saliva is a mixture of fluids secreted mainly by the three pairs of major salivary glands: parotid, submandibular, and sublingual. The 400 to 500 small salivary glands distributed over the buccal mucosa (except in the gums and anterior half of the hard palate), lips, and along the mucosa of the upper aerodigestive tract, present in the nasal cavity to the larynx and pharynx, also participate in this secretion.<sup>1,2</sup> Together, they are responsible for the remaining 5% of saliva secreted by humans.<sup>3</sup> The saliva secreted by the major glands differs in composition; it is considered that humans secrete approximately 0.5 liters of saliva per day in response to stimulation of the sympathetic and parasympathetic autonomic nervous system.<sup>4</sup>

A reduction in salivary flow (hyposalivation) is a common disorder: it is estimated that approximately 20% of the general population have this alteration.<sup>5</sup> It is natural for humans to go through short periods of hyposalivation, and its occurrence is frequent when individuals are under psychological stress.<sup>6,7</sup> Changes of fluids and electrolytes, as occurring in diabetes mellitus, hypothyroidism, and low hydration can also cause reduced salivary flow. However, hyposalivation may be due to multiple causes, which may include involvement of the glandular parenchyma by infectious, inflammatory processes, whether associated or not with granulomatous diseases or autoimmune conditions (such as Sjögren's syndrome and rheumatoid arthritis);<sup>2,8</sup> radiotherapy of the head and/or cervical region;<sup>9,10</sup> or it may be associated with mood disorders;<sup>6</sup> adverse effects caused by the use of some medications;<sup>6</sup> or it

can also be idiopathic.<sup>11</sup> The decrease in flow and alterations in salivary composition affects 25% of the elderly population, and complaints of oral and systemic discomfort due to these alterations are common.<sup>12</sup>

Conventional therapies for the treatment of reduced salivary flow using chemical and gustatory secretagogues are still limited. However, new alternatives have shown great perspective for the treatment of this disorder.<sup>13,14</sup>

To diagnose a patient with chronic hyposalivation is a challenge in clinical practice,<sup>15</sup> due to lack of medical records indicating the patient's salivary pattern.<sup>16</sup> However, the serial assessment of salivary flow is important for the diagnosis and prognosis of certain oral and systemic conditions.<sup>17,18</sup> It has been stated that health professionals have not yet adopted this practice due to the lack of availability of simple evaluation procedures.<sup>18-20</sup> As a result, hyposalivation goes undiagnosed in asymptomatic patients. Conversely, some patients may be misdiagnosed as having dry mouth when xerostomia (dry mouth sensation) is not accompanied by a decrease in the salivary secretion rate.<sup>21</sup>

This review aimed to address some issues related to the role of saliva, the consequences of hyposalivation, and methods of salivary flow rate measurement, which are useful concepts in the daily practice of rheumatology.

## Functions of saliva

Saliva has many functions (Table 1) related to the maintenance of oral and systemic integrity,<sup>22</sup> and it is critical for the first line of oral defense.

However, the complexity of the molecular composition of saliva has shown its importance in the systemic context. Saliva acts in the maintenance of the upper gastrointestinal tract pH.<sup>23</sup> Additionally, it has defense factors such as antibodies, cytokines, and growth factors that are associated with defense mechanisms and healing of inflammatory and infectious processes not restricted to the mouth, but also including the oropharynx, esophagus, and stomach.<sup>24-28</sup>

**Table 1 – Functions of saliva and its components.**

Function	Effect	Active constituents
Tissue repair	Healing of the oral and gastric mucosa and oropharynx	Epidermal growth factor (EGF)
Protection	Lubrication of the mouth, oropharynx, and esophagus Impermeabilization Washing Film formation	Glycoproteins  Water
Tamponage	Maintaining of unfavorable pH for micro-organism colonization Neutralization of acidity	Phosphate, bicarbonate, and proteins
Digestion	Formation of the food bolus Neutralization of esophageal contents Digestion of starch, proteins, and lipids	Mucin and water Phosphate and bicarbonate Amylase, protease, and lipase
Gustation	Solubilization of molecules Maturation of taste buds	Water Gustine and Zn <sup>++</sup>
Antimicrobial action	Barrier  Antibodies Bacterial antagonism  Antiviral activity	Glycoprotein  IgA, IgM, and IgG Lysozyme Lactoferrin System of peroxidase, cystatin, mucin, and immunoglobulins
	Antifungal activity	Histatin, chromogranin A, and immunoglobulins
Tooth integrity	Maturation of the enamel Protection against demineralization Remineralization	Calcium and phosphate Mucins, calcium, and phosphate Proteins rich in proline, staterine, calcium, and phosphate
Antioxidant defense system	Prevents the formation of free radicals, eliminates existing free radicals, and repairs damage that has occurred	Uric acid, albumin, a-tocopherol, b-carotene, glutathione, and ascorbate

Cate, 1998;<sup>53</sup> Amerogen and Veerman, 2002<sup>54</sup> (adapted).

Salivary components interact with microorganisms and are important to control the composition of the oral microbiota.<sup>26</sup> In this context, it is noteworthy that patients sedated in intensive care units often have alterations in salivary patterns within just two weeks of hospitalization. It is observed that most of these patients have elevated Gram-negative oral microbiota, and that there is also a high occurrence of nosocomial pneumonia. Thus, a correlation between salivary alterations and the manifestation of nosocomial pneumonia has been established.<sup>29</sup>

### Consequences of hyposalivation

In a systematic review of the subject, it was concluded that the flow rate of stimulated whole saliva below the normal range (< 1.0 mL/min of stimulated saliva) can be considered a predictor of caries.<sup>30</sup> Regarding the degree of formation of dental calculus, it is known that it depends on the rate of salivary gland secretion, and a low salivary flow, associated with high salivary viscosity, would be a risk factor for periodontal disease in the elderly.<sup>31</sup>

Saliva also reflects the control of water consumption by the body, since when the body is dehydrated, the mouth becomes dry, and thirst is felt.<sup>32,33</sup> It was observed that patients with severe hyposalivation tend to ingest more fluids during the day and night. Thus, they are likely to wake up at night more often to drink water and urinate. These frequent interruptions in nighttime sleep may favor insomnia, depression, and decreased memory, which affect the individual's quality of life.<sup>34</sup>

Moreover, it appears that severe hyposalivation is associated with increased occurrence of opportunistic fungal infections in the mouth and oropharynx, stomatitis, difficulty to eat dry solids, dysphagia, burning sensation in the tongue and other parts of the oral mucosa, rampant caries, dental biofilm, instability of total dentures, dysgeusia, and halitosis.<sup>24,35-38</sup> Another important aspect is also related to changes in eating habits, since the lack of saliva can reduce the pleasure of eating due to reduced sense of taste.<sup>38,39</sup> Therefore, hyposalivation can result in physical, functional, and social impairment, affecting the quality of life of patients.<sup>10,40</sup>

Regarding social and quality of life impairment, it is known that halitosis results in severe emotional disorders for patients.<sup>41,42</sup> Fisher (1915) stated that bad breath can be sexually disgusting by indicating a variety of diseases.<sup>43</sup> Saliva represents a systemic body fluid that contains, among others, volatile organic compounds (VOCs). These compounds are considered to be excellent indicators of environmental and occupational exposure to chemicals, resulting from transdermal absorption, inhalation, or through food intake.<sup>44</sup> VOCs from the saliva have been used in physiological, metabolomic, pharmacokinetic, toxicological, and forensic studies.<sup>44</sup> Moreover, classic<sup>45,46</sup> and current studies<sup>47,48</sup> state that halitosis, in most cases, originates in the mouth and results from the metabolism of proteolytic anaerobic bacteria that release volatile sulfur compounds (VSCs).

Saliva is essential not only for the dilution of these compounds, but also to provide the washing of the oropharynx, thus hindering the stagnation of organic matter and con-

sequent formation of disagreeable gaseous compounds. It is worth noting that, depending on the capacity of volatilization of these compounds, they may or may not stimulate the human sense of smell. In this context, it is important to emphasize that halitosis is a perceived change in the quality of the expiratory flow odor. Therefore, it can manifest as a signal, clinical halitosis, noticeable by the examiner and the people living with the individual that has halitosis, or as a symptom, i.e., subclinical halitosis, perceptible only by the patient.<sup>37</sup>

Subclinical halitosis represents a major challenge in routine clinical care, and causes major behavioral changes due to the patient's belief that he/she has bad breath and the difficulty in establishing an accurate diagnosis.<sup>47</sup> This situation may occur due to the low concentration of volatile compounds that excite the retronasal endings of the individual, the sense of bad taste, or due to psychiatric disorders such as olfactory reference syndrome. Nevertheless, it appears that individuals with severe hyposalivation and asialia are vulnerable to gustatory sense-perceptive disorders that cause an unpleasant taste.<sup>49</sup>

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### Salivary flow assessment methods

Tests used in the screening of a risk factor in the diagnosis of disease and in estimating the prognosis of a patient are important and costly phases of healthcare, and thus, they are noteworthy in clinical research.<sup>50</sup>

Several methods have been proposed for salivary flow assessment. The choice of technique can be made by collecting whole saliva or saliva from a specific salivary gland. In addition, a sample can be obtained to evaluate salivary flow with and without stimulus.

Whole saliva is a multiglandular secretion complex consisting of gingival fluid, desquamated epithelial cells, microorganisms, products of bacterial metabolism, food debris, leukocytes, and mucus from the nasal cavity and the pharynx.<sup>26</sup> Its main advantage as part of the clinical evaluation is its ease-of-collection, and it is more often used than the individualized sample.

Regarding the absence or presence of stimulation in the evaluation of salivary flow, the former will primarily reflect the functional status of the submandibular and sublingual glands, as these are mainly responsible for basal secretion. However, the nature of the stimulus will influence the type of response. Mechanical stimulation promotes a marked response of the parotid gland, while gustatory stimulus activates the three pairs of major salivary glands. Table 2 shows different methods used to evaluate the rate of whole saliva flow.

The passive flow method has been frequently used for the assessment of unstimulated saliva in clinical practice. With regard to stimulation, the mechanical stimulus has been more often used. A five-minute collection time has been widely used to evaluate the flow rate of unstimulated and stimulated saliva.

Table 3 shows the values found for the flow rate of unstimulated whole saliva and under different types of stimuli, demonstrating the inter- and intra-patient variability. In addition to the technique, other factors may influence the

results obtained, such as ambient temperature, relative air humidity, noises in the environment, time of sampling, duration of collection, type of gustatory stimulation, consistency and size of the mechanical stimulus, fasting period, environment brightness, and even the season of the year.<sup>17,51,52</sup> These factors should be controlled as much as possible, and a test standardization should be used so as not to impair test result reliability.

Table 4 shows the reference values to classify patients as having severe or mild hyposalivation, or normosialia. Prior to collection, the patient should be instructed not to smoke, eat, drink, or perform any oral hygiene procedures in the two hours prior to the measurement. In addition, the patient should drink 300 mL of water two hours prior to collection of saliva to prevent the variability in body hydration from affecting the results. Another important aspect concerns the standardization of time, i.e., flow monitoring should always be performed at the same time at which the first collection was performed, in order to avoid circadian variations. It is important that the clinical environment should be peaceful and that the patient should turn the phone off, because otherwise the ring or other sound from the device can generate anxiety and alter the results. Regarding the evaluation sequence, the unstimulated saliva flow should be assessed first, and then the salivary flow rate in response to stimulation.

The professional must strive to include this assessment as part of routine care in cases where the patient will be submitted to treatments that can promote changes in salivary flow. As examples, prior to prescribing xerogenic medications in addition to chemo- and radioiodine therapy, in cases where patients will undergo radiation therapy in the cervical-encephalic region, when suspecting and monitoring the progression of autoimmune diseases, and in other situations of dental interest.

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### Conclusions

Saliva has many functions, including tissue repair, tamponage, mechanical protection, digestion, taste, antimicrobial action, and maintenance of tooth integrity and the antioxidant defense system. Hyposalivation can result in physical, functional, and social impairment, causing a negative impact on quality of life of patients.

As an organic fluid, which varies according to a number of factors and circumstances, the use of the assessment of salivary flow in clinical practice requires standardization of its performance.

Therefore, it is important for the rheumatologist to know the functions of saliva, the consequences of hyposalivation, and the methods of salivary flow assessment, since diagnosing a patient with chronic hyposalivation is a challenge in clinical practice and serial evaluation of salivary flow is important for the diagnosis, prognosis, and monitoring of certain systemic and oral conditions.

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### Conflicts of interest

The authors declare no conflicts of interest.

**Table 2 – Proposed methods to evaluate whole saliva flow.**

Type whole saliva	Methods	Measurement technique*	Advantages	Disadvantages
Without stimulus	Passive drainage	Saliva flows passively from the mouth into a graduated container	- Reproducible - Reliable to measure salivary flow	- Evaporation of saliva
	Active drainage	The saliva accumulated in the mouth must be regularly expectorated into a graduated container	- Reproducible - Reliable to measure salivary flow	- Evaporation of saliva - There is a small stimulation of salivary flow in the act of spitting
	Suction	Saliva pooled on the mouth floor is vacuumed and accumulated in a graduated container	Does not depend on patient collaboration	- There is a small stimulation of salivary flow
	Absorption	Swab, cotton, or gauze roll, pre-weighed, is inserted into the mouth for a certain amount of time and later weighed again	Detects the presence of saliva in the oral cavity, using a simple and easy method, especially in outpatient clinics and dental offices	- There is a small stimulation of salivary flow - Less reliable method - Alters the concentration of some salivary components
With stimulus	Mechanical	To chew paraffin, silicone, or unflavored chewing gum and spit the saliva into a graduated container	- Absence of side effects - There is no contamination of saliva with exogenous substances	The frequency of mastications must be standardized with the aid of a metronome
	Gustatory	Applying citric acid to the lateral borders of the tongue		It can interfere with the analysis of some salivary components
	Absorption	-The swab is inserted into the mouth to be chewed for a certain time and subsequently weighed	Detects the presence of saliva in the oral cavity using a simple and easy method, especially in outpatient clinics and dental offices	There is a small stimulation of salivary flow - Less reliable method - Alters the concentration of some salivary components

Vissink et al, 2008<sup>55</sup> (adapted).

**Table 3 – Flow rate of whole saliva.**

Author (year)	Flow rate		Participants			Type of stimulus	
	N/S	W/S	N	Age	Gender		
Becks and Wainwright (1943) <sup>56</sup>	0.32 (0.23)	2.0 (0.9)*	484	50*	5-49	M + F	Paraffin
Bergdahl (2000) <sup>57</sup>	0.33 (0.26)	2.5 (1.06)	669		20-69	M	Paraffin
	0.26 (0.21)	2.02 (0.93)	758		20-69	F	Paraffin
Engelen et al. (2003) <sup>58</sup>	0.45 (0.18)	1.22 (0.52)	8		19-33	M	Paraffin
		0.50 (0.24)					Odor
		2.69 (1.92)					Citric acid
	0.35 (0.17)	1.06 (0.40)	14		19-33	F	Paraffin
	0.52 (0.20)					Odor	
	2.06 (0.68)					Citric acid	
Eliasson et al. (2006) <sup>59</sup>	0.3 (0.2)	2.4 (1.3)	46		22-82	M	Paraffin
	0.2 (0.2)	1.8 (0.8)	96		18-81	F	Paraffin

N/S, no stimulus, W/S, with stimulus, M, male; F, female.

Flow rate mL / min (standard deviation).

**Table 4 – Classification of whole saliva flow rate.**

Whole saliva flow rate (mL/min)	Very low	Low	Normal
Without stimulus	< 0.1	0.1-0.25	> 0.25
With stimulus	<0.7	0.7-1.0	> 1.0

Source: Ericsson and Hardwick, 1978.<sup>60</sup>



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