

THE ONTOGENY OF SALIVA SECRETION IN INFANTS AND ESOPHAGOPROTECTION

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ABSTRACT - Background - Several studies have reported that severe reflux esophagitis is rare in infants despite the well known high occurrence of regurgitation in early infancy. There is evidence of the importance of saliva for the pre-epithelial protection of the esophageal mucosa. **Results** - A longitudinal study conducted on healthy infants indicated that the stimulated capacity of saliva secretion (saliva output per kg of body weight) was significantly higher during their first year of age compared to older children and adults. In addition, this secretion pattern was also observed in low weight newborns during the first weeks of life and persisted in infants with severe protein-calorie malnutrition (marasmus). **Conclusion** - The greater ability to secrete saliva is an important physiological condition that may protect the infant from acid/pepsin aggression to the esophagus during early stages of development. **HEADINGS** - Infant. Gastroesophageal reflux. Salivation. Saliva.

INTRODUCTION

Saliva, the name given to the mixture of fluids produced by the salivary glands, has multiple functions in the processes that occur in the upper part of the gastrointestinal tract⁽⁴⁴⁾. Updated information about the process of salivary secretion is available in the recent literature⁽¹⁰⁾.

Changes in saliva volume and/or composition have been reported in various pathological conditions affecting children, such as reduced volume and concentration of salivary amylase in children with kwashiorkor⁽¹¹⁻¹³⁾; reduced salivary amylase in children with second-degree protein-calorie malnutrition⁽⁷⁰⁾; significant reduction of stimulated and non-stimulated salivary flow in adolescents who had been severely malnourished when children⁽⁴⁵⁾; moderate to marked reduction of IgA concentration in saliva in children with severe protein-calorie malnutrition (kwashiorkor and marasmus)^(46, 69); reduced non-stimulated salivary flow and pH in type 1 diabetes mellitus⁽³⁶⁾; reduced salivary amylase concentration in obese boys compared to controls of the same sex but not when compared to girls⁽⁴⁰⁾; increased secretion of calcium, protein, amylase and calcium-containing zymogen granules in stimulated submandibular salivary secretion⁽²⁾ and increased sodium and chloride concentration⁽²²⁾ in the saliva of patients with cystic fibrosis; reduction of salivary flow rate, of amylase and K⁺ concentration with increased Na⁺ concentration and greater buffering capacity of saliva in children with Down syndrome

compared to controls of the same age^(57, 58), among others. The clinical prevalence of drooling of saliva is high among children with cerebral palsy^(32, 35). In this serious condition of involvement of the central nervous system, drooling is not a consequence of hypersalivation, but rather of difficulty in swallowing saliva⁽⁶¹⁾ and the reduced flow rate and increased salivary osmolality seem to be caused by reduced fluid intake⁽⁵⁰⁾.

Functions of saliva in the oral cavity

Particularly important among the multiple functions of saliva in the oral cavity are solubilization, formation of the food bolus, identification of flavors, facilitation of mastication and swallowing; clearance of bacteria and food; lubrication of the mucosa, and facilitation of speech. In addition, saliva acts on tooth protection by buffering acids, on the maintenance of a high concentration of calcium phosphate, and on the formation of a protective film on the dental surface⁽⁴⁴⁾.

Function of saliva in the esophagus

Because of its buffering capacity and its content of pre-epithelial defense factors, this exocrine secretion acts on the protection and repair of the esophageal mucosa in situations of aggression such as the presence of gastroesophageal reflux (GER)^(42, 51, 52). There is evidence that salivary bicarbonate is the most important protective factor for the esophageal mucosa against acid/peptic aggression in GER⁽⁵⁹⁾.

Declared conflict of interest of all authors: none

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Gastroesophageal reflux

GER is the return of gastric content to the esophagus. The intermittent opening of the lower esophageal sphincter, regardless of the deglutition process, is the most frequent cause of GER in children and adults⁽⁶⁶⁾. GER disease (GERD) is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications⁽⁶³⁾. In infancy, GER accompanied by esophagitis, apnea, chronic respiratory disease, growth deficit or other manifestation represents GERD⁽⁵⁾. There is evidence of a genetic influence on the development of GERD^(34,41). The most common manifestation of esophageal injury is reflux esophagitis⁽⁵⁾. The determinant factors of esophagitis include the frequency of GER, the volume of refluxed gastric content, the potency of the refluxed material, efficacy of esophageal clearance, and the resistance of esophageal tissue to aggression⁽¹⁸⁾.

GER may be occult or may manifest through objective symptoms such as regurgitation and/or vomiting. In infants, regurgitation as a visible expression of GER is frequent and most of the times has a benign course. A survey of parents of healthy American infants during the first year of life indicated the occurrence of at least one daily episode of regurgitation in 50% of infants aged 0-3 months, with a peak at 4-6 months (67%), a frequency that was drastically reduced to 5% at 10-12 months⁽³⁸⁾. Another comparable study also concluded that regurgitation is a common symptom among Japanese infants and is reduced with age⁽³³⁾. In addition, several studies evaluating the reflux index (percent time during which pH was less than 4 in 24-hour esophageal pH monitoring) suggest that acid reflux is a physiological process more frequently occurring in healthy infants than in healthy adults⁽⁴⁹⁾.

On the other hand, several studies have reported that severe reflux esophagitis is rare in infants, especially in those aged less than 6 months^(16, 21, 56, 64). The natural history of GER in infants, managed with conservative treatment⁽⁹⁾ or with active therapy⁽⁵⁵⁾, shows that its course is benign in most cases, whereas 5% and 2% of the infants, respectively, develop esophageal strictures. Though a stricture has been described to occur as early as at 3 days and 3 months, it is unusual for a fibrous stricture to develop before 2 years of age⁽⁸⁾.

The consequences of esophageal stricture for a child are dramatic. Thus, efficient methods of diagnosis and treatment have been developed over the last decades in order to control this and other complications of GERD^(29, 67).

It is intriguing to observe the high frequency of regurgitation in infants and its relative "benign" nature with respect to the occurrence of esophageal disease.

Some factors may explain this phenomenon. The first is related to the potency of the refluxed material. After stimulation of gastric secretion with betazole, acid output (mEq/kg/h) and pepsin-equivalent output (mg/kg/h) were low in newborns and, at 67-110 days of life, reached values corresponding to half those observed in adults⁽¹⁾. At 6 months of life, the production of gastric acid (mEq/kg/h) was similar to

that observed in children aged 4-9 years and in adults^(4, 23). The second is milk, the predominant food during this phase of life which by its buffering power protects the esophagus from acid/pepsin aggression⁽⁶⁰⁾. It has been suggested that breast-feeding may have a better protective effect than artificial feeding^(6, 24). As a third factor, we point out the participation of salivary secretion. Among these functions is the important participation of saliva as a component promoting esophageal clearance (by the swallowing stimulus), buffering (mainly based on bicarbonate) and dilution of refluxed acid, thus reducing the exposure of the esophageal mucosa to aggression^(3, 18, 25). The importance of saliva as a factor of esophageal protection is clearly demonstrated by the fact that the promotion of salivation increases the salivary protective components and the number of swallows and reduces the time of exposure of the esophageal mucosa to acid/pepsin^(26, 28, 37, 43, 53). Also, patients with esophagitis have a lower saliva secretion compared to controls^(7, 27) and a lower response to mechanical and chemical stimulation of the epithelial growth factor secreted in the saliva of patients with reflux esophagitis⁽⁴⁸⁾.

Regarding the relationship between an acid stimulus and saliva production, two facts are known: 1) the application of acid to the oral mucosa is a potent stimulus of salivary secretion⁽⁴⁴⁾ and 2) the exposure of the esophageal mucosa to hydrochloric acid determines a rapid salivation, probably mediated by pH-sensitive receptors located in the esophageal mucosa⁽¹⁹⁾.

Ontogeny of salivary secretion in infants

Studies of stimulated or non-stimulated saliva secretion in children are fragmented and scarce, corresponding to some age ranges^(62, 68), or representing a secondary result of the study of production of salivary amylase or of other saliva components⁽¹⁷⁾ or of parotid secretion alone⁽³¹⁾. Other studies have evaluated the production of salivary amylase without reporting the saliva volume produced^(39, 47, 54). These studies do not provide a view, even in rough terms, of how saliva secretion evolves during the first months of life of an infant, described as "abundant" by both lay people and health professionals.

Three decades ago we conducted a longitudinal study of saliva and salivary amylase secretion on 10 infants during the first year of life⁽¹⁵⁾. The infants were neonates born at term and with adequate growth and development patterns. Saliva was collected at 1, 15, 30, 45, 60, 90, 120, 150 and 160 days and then at 9 and 12 months of age. For the age in days (except for day 1) the maximum tolerance permitted for saliva collection was ± 2 days in relation to the scheduled date, whereas for 9 and 12 months the tolerance was one week. None of the infants presented acute or chronic infectious processes on the occasion of saliva collection. The rigorous schedule of the collection dates as well as other reasons caused only 10 of the 36 newborns initially admitted to the study to reach the end of the observation period. The results were compared with those obtained for a group of 18 healthy children aged 1.6-3 years and a group of 18 healthy adults aged 20-30 years.

Briefly, the technique used, modified from Rossiter et al.⁽⁴⁷⁾, was as follows: 1) saliva was collected between 10:00 and 12:00 a.m. 30 minutes or more after the last feeding; 2) the collection of saliva was started 15 seconds after stimulation with one drop of lemon juice applied to the dorsum of the tongue; 3) all the saliva secreted into the oral cavity was collected by continuous gentle aspiration for 5 minutes (5 min) using a flexible catheter connected to a calibrated syringe, both of them sterilized⁽¹¹⁾.

It can be seen in Figure 1 that the saliva volume secreted (mL/5 min) (upper graph) is small in newborns, later increasing and reaching maximum values between 3 and 6 months and then decreasing at 1 year of age to values comparable to those observed in older children. On the other hand, saliva output in $\mu\text{L}/5 \text{ min}/\text{kg}$ (lower graph) was relatively high at birth compared to children aged 1.6-3 years, reaching extraordinarily high values between 3 and 6 months of life. We also observed that this pattern occurs in low weight newborns during the first weeks of life⁽¹⁴⁾ and persists in infants with severe primary protein-calorie malnutrition (marasmus)⁽²⁰⁾.

Saliva and esophagoprotection in infants

To define the participation of saliva in esophageal protection during the first months of life it is necessary to answer

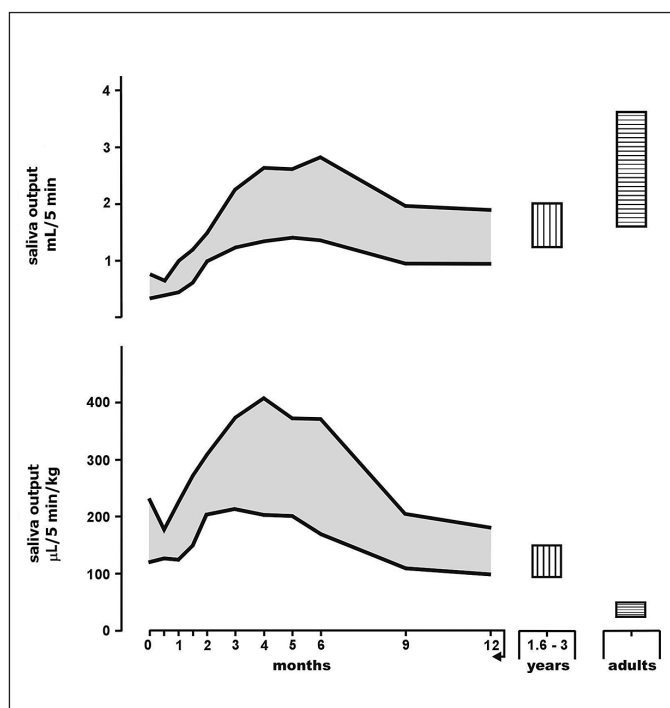


FIGURE 1. Saliva output of infants during the first year of life (longitudinal study) compared to older children (1.6-3 years of age) and young adults, all of them healthy. The upper graph represents the saliva volume secreted over a period of 5 minutes (5 min) after stimulation with one drop of lemon juice (mL/5 min). The lower graph represents saliva output in $\mu\text{L}/5 \text{ min}/\text{kg}$. Values are expressed as 95% confidence intervals. Modified from Collares EF, Brasil MRL and Kawazaki ST⁽¹⁵⁾, with permission.

the following question: is the infant's capacity for saliva secretion the same as for other ages?

An analysis of Figure 1 permits us to conclude that in no other phase of life is the rate of production of this exocrine secretion per kg weight as intense as during the first year of age!

Here we must ask whether saliva is important for esophagoprotection in infants.

Although the reason for this greater saliva output in infants is still unknown, it is reasonable to assume that the phenomenon may be an adaptive response to stimulation of the sensory nerve ends of the esophagus and of the oral cavity by the acid of the refluxed gastric content (regurgitation), more intense during this phase of life. Although obtained in distinct types of study, some evidence in this respect is that during the first months of life a temporal relation can be observed between the increase capacity of saliva secretion and the elevation of acid secretion by the gastric mucosa^(1, 4, 23), a higher frequency of regurgitations^(33, 38), and the course of the reflux index in healthy infants during the first year of life⁽⁶⁵⁾.

A greater production of saliva may provide, in addition to the possibility of a higher acid-buffering capacity, a greater quantity of other pre-epithelial defense factors already identified in this secretion and which have been pointed out as possible participants in the protection and repair of the esophageal mucosa^(42, 51, 52). However, no information is available about the evolution, efficiency and degree of participation of the factors of pre-epithelial esophageal mucosal protection against acid/pepsin aggression during the first year of life.

In conclusion, the greater ability to secrete saliva after a stimulus, a phenomenon characteristic of the first months of life, may be an important physiological condition that must protect the infant, at least in part, from acid/pepsin aggression to the esophagus.

Final comments

The study of salivary secretion is neglected by medical doctors and by gastroenterologists in particular. Most of the available literature reports have been produced by investigators working in the area of oral health. The evidence of the importance of saliva and its components acting on the pre-epithelial protection of the upper digestive tract indicates a promising field of investigation among infants. In addition, it should be emphasized that, over the last decade, this fluid of easy acquisition has been used for the diagnosis and monitoring of some human diseases⁽³⁰⁾ and studies aiming at its utilization in infants should take into consideration the understanding of the ontogeny of this secretion.

Authors' contributions

Collares EF and Fernandes MIM participate equally in the manuscript writing processes.

Collares EF, Fernandes MIM. A ontogenia da secreção de saliva em lactentes e a proteção pré-epitelial do esôfago. *Arq Gastroenterol.* 2015;52(2):156-60.

RESUMO - Contexto - Vários estudos têm indicado que a esofagite de refluxo é rara em lactentes no primeiro ano de vida a despeito da elevada ocorrência de regurgitação nesta fase da vida. Há evidências da importância da saliva para a proteção pré-epitelial da mucosa esofágica. **Resultados** - Um estudo longitudinal conduzido em lactentes saudáveis indicou que a capacidade estimulada da secreção de saliva (volume de saliva/kg de peso) foi significativamente elevada no primeiro ano de vida comparada com crianças com mais idade e adultos jovens. Este padrão também foi observado nas primeiras semanas de vida de recém-nascidos com baixo peso e persistiu em lactentes com desnutrição proteico-calórica grave (marasmo). **Conclusão** - A grande habilidade para secretar saliva é uma importante condição fisiológica que pode proteger o lactente da agressão ácido/péptica do esôfago durante os primeiros estágios do seu desenvolvimento.

DESCRITORES - Lactente. Refluxo gastroesofágico. Salivação. Saliva.

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Received 30/9/2014
Accepted 18/12/2014