The rôle of saliva in maintaining oral health and as an aid to diagnosis

Carmen Llena Puy

Primary Health Care Dentist. Department 9. Valencian Health Service. Lecturer in Preventive Dentistry. CEU Cardenal Herrera University

Correspondence:
Dra. Carmen Llena Puy
C/Albuixech nº 8, pta.2
46021 Valencia
Tf: +34963604877
E-mail:llena@uv.es

Llena-Puy C. The rôle of saliva in maintaining oral health and as an aid to diagnosis. Med Oral Patol Oral Cir Bucal 2006;11:E449-55.
© Medicina Oral S. L. C.I.F. B 96689336 - ISSN 1698-6946

Received: 29-03-2006
Accepted: 20-05-2006

Indexed in:
-Index Medicus / MEDLINE / PubMed
-EMBASE, Excerpta Medica
-Indice Médico Español
-IBECS

Click here to view the article in Spanish

ABSTRACT

Saliva is a complex secretion. 93% by volume is secreted by the major salivary glands and the remaining 7% by the minor glands. 99% of saliva is water and the other 1% is composed of organic and inorganic molecules. While the quantity of saliva is important, so is its quality.

The components of saliva, its functions in maintaining oral health and the main factors that cause alterations in salivary secretion will be reviewed, the importance of saliva in caries development and bacterial plaque formation will be discussed and its rôle as an aid to diagnosing certain pathologies will be examined.

Variations in salivary flow can be affected, reversibly or irreversibly, by numerous physiological and pathological factors. Saliva plays an essential rôle in maintaining the integrity of the oral structures, in personal relationships, in the digestion and in controlling oral infection. The part that saliva plays in protecting teeth from caries can be summarised under four aspects: diluting and eliminating sugars and other substances, buffer capacity, balancing demineralisation / remineralisation and antimicrobial action.

Saliva is a promising option for diagnosing certain disorders and monitoring the evolution of certain pathologies or the dosage of medicines or drugs. Its advantages as a diagnostic tool include its being easy to obtain and the positive correlation between many parameters in serum and saliva.

Key words: *Saliva, hypersalivation, hyposalivation, caries, bacterial plaque, diagnosis.*

RESUMEN

La saliva es una secreción compleja proveniente de las glándulas salivales mayores en el 93% de su volumen y menores en el 7% restante. El 99% de la saliva es agua mientras que el 1% restante está constituido por moléculas orgánicas e inorgánicas. Si bien la cantidad de saliva es importante, también lo es la calidad de la misma.

Se revisará los componentes de la saliva y sus funciones en el mantenimiento de la salud oral los principales factores causales que alteran la secreción salival, se comentará la importancia de la saliva en el desarrollo de la enfermedad de caries y en la formación de la placa bacteriana, y se analizará su papel como material de ayuda para el diagnóstico de algunas patologías.

Las variaciones en el flujo salival pueden verse afectadas por múltiples factores fisiológicos y patológicos, de forma reversible o irreversible. Juega un papel fundamental en el mantenimiento de la integridad de las estructuras bucales, en la vida de relación, en la digestión y en el control de infecciones orales. El papel de la saliva en la protección frente a la caries podemos concretarlo en cuatro aspectos, dilución y eliminación de los azúcares y otros componentes, capacidad tampón, equilibrio entre la desmineralización / remineralización y acción antimicrobiana.

La saliva como alternativa para el diagnóstico, de algunas enfermedades, como elemento para monitorizar la evolución de determinadas patologías o la dosificación de medicamentos o drogas proporciona una vía prometedora. La accesibilidad en su obtención y la correlación positiva entre múltiples parámetros en el suero y en la saliva son algunas de las ventajas que ofrece como instrumento diagnóstico.

© Medicina Oral S.L. Email: medicina@medicinaoral.com

Palabras clave: *Saliva, hiposialia, caries, placa bacteriana, diagnóstico.*

INTRODUCTION

Saliva is a complex secretion. 93% by volume is secreted by the major salivary glands and the remaining 7% by the minor glands. These glands are located in every region of the mouth except for the gums and the anterior part of the hard palate. Saliva is sterile when it leaves the salivary glands but ceases to be so as soon as it mixes with the crevicular fluid, remains of food, microorganisms, desquamated oral mucous cells, etc. (1).

The salivary glands are made up of acinar and ductal cells. The acinar cells of the parotid gland produce a largely serous secretion. While this gland synthesises most of the alpha-amylase, it produces less calcium than the submandibular gland. The mucins are mainly produced by the submandibular and sublingual glands and proline- and histatin-rich proteins by the parotid and submandibular glands. The minor salivary glands are essentially mucous.

Daily secretion rates range between 500 and 700 ml and the average volume in the mouth is 1.1 ml. Saliva production is controlled by the autonomous nervous system. At rest, secretion ranges from 0.25 to 0.35 ml/min and is mostly produced by the submandibular and sublingual glands. Sensory, electrical or mechanical stimuli can raise the secretion rate to 1.5 ml/min. The greatest volume of saliva is produced before, during and after meals, reaching its maximum peak at around 12 a.m., and falls considerably at night, while sleeping (2).

99% of saliva is water and the other 1% is composed of organic and inorganic molecules. Saliva is a good indicator of the plasma levels of various substances such as hormones and drugs and can therefore be used as a non-invasive method for monitoring plasma concentrations of medicines or other substances (3).

This paper will review the components of saliva, its functions in maintaining oral health and the main factors that cause alterations in saliva secretion. It will then show its part in protecting against caries and bacterial plaque formation and examine its rôle as an aid to diagnosing certain pathologies.

CLINICAL IMPORTANCE OF THE QUANTITY AND QUALITY OF SALIVA IN MAINTAINING ORAL HEALTH

While the quantity of saliva is important, so is its quality, as each of its components performs a series of specific functions (summarised in table 1).

The normal quantity of saliva can be reduced. This is known as hyposalivation or hypoptyalism and significantly affects the individual's quality of life as well as his or her oral health. The main symptoms and signs associated with hyposalivation are a 'dry mouth' feeling or xerostomia, frequent thirst, difficulty in swallowing, difficulty in speaking, difficulty in eating dry foods, the need to drink water frequently, difficulty in wearing dentures, pain and irritation of the mucosa, a burning feeling in the tongue and dysgeusia. The signs most frequently encountered are loss of glossiness of the oral mucosa, dryness of the mucosa, which become thin and cracked, fissures in the dorsum of the tongue, angular cheilitis, thick saliva, increased frequency of oral infection, especially by *Candida* spp., presence of caries in atypical locations and increased size of major salivary glands (4).

The diagnosis of salivary gland hypofunction is based on data derived from the symptoms reported by the patient, clinical examination leading to verification of the above-mentioned clinical signs and quantitative sialometry (measurement of salivary flow). Detemining the aetiology of this hypofunction sometimes requires additional examination by means of image diagnosis, which nowadays essentially means magnetic resonance (MR) or a histological study following a biopsy (5).

Less frequently, salivary secretion can increase. This is called hypersalivation, ptyalism or sialorrhea and it may be physiological or pathological. It is diagnosed through the symptoms reported by the patient, who suffers the inconvenience of constantly having to swallow saliva or, in patients with cerebral palsy or other severe neurological disorders, constant drooling that causes frequent chapping of the lips and of the skin of the face and neck, with the risk of secondary infection. Sialometry will demonstrate an increase in the unstimulated salivary flow rate (6).

Table 1. Saliva components and functions (4).

Functions	Components
Lubrication	Mucin, proline-rich glycoproteins, water
Antimicrobial action	Lysozyme, lactoferrin, lactoperoxides, mucins, cystins, histatins, immunoglobulins, proline-rich glycoproteins, IgA
Maintaining mucosa integrity	Mucins, electrolytes, water
Cleansing	Water
Buffer capacity and remineralisation	Bicarbonate, phosphate, calcium, staterin, proline-rich anionic proteins, fluoride
Preparing food for swallowing	Water, mucins
Digestion	Amylase, lipase, ribonucleases, proteases, water, mucins
Taste	Water, gustin
Phonation	Water, mucin

© Medicina Oral S.L. Email: medicina@medicinaoral.com

MAIN CAUSES OF HYPO AND HYPERSALIVATION

A number of physiological circumstances reduce salivary secretion. They include age, the number of teeth in the mouth, male/female, body weight and the time of day. In relation to age, although submaxillary and sublingual gland secretion may be slightly diminished in older persons, the same cannot be said of the parotid glands, and a reduction in the unstimulated total saliva but good response to stimulation may be observed despite the presence of other factors such as polymedication or certain disorders such as diabetis, dehydration, hypertension, etc. which may aggravate the clinical symptoms (7, 8).

Other pathological conditions also affect salivary flow. Over 400 medicines, many of them in common use, induce salivary gland hypofunction. Table 2 shows the drug groups that have been most directly linked to salivary hyposecretion (4). Head and neck radiotherapy causes irreversible hyposalivation by destroying the glandular parenchyma. The adverse effects start from 4000 rads onwards and the reduction in salivary flow depends on the dose (9). Some systemic disorders cause progressive destruction of the salivary glands, as in some autoimmune diseases such as Sjögren's syndrome (10), while others lead to vascular or neurological alterations that have transitory and reversible repercussions on saliva production, as in hypertension, depression, malnutrition, dehydration, diabetis, etc.

Table 2. Medicines and drugs with side effects on salivary secretion (4)

Medicine group	Examples
Anorectic	Fenfluramine
Anxiolytics	Lorazepam, diazepam
Anticonvulsants	Gabapentin
Antidepressants - Tricyclic	Amitriptyline, imipramine
Antidepressants - SSRI	Sertraline, fluoxetine
Antiemetics	Meclizine
Antihistaminics	Loratadine
Antiparkinsonian	Biperidene, selegiline
Antipsychotics	Clozapine, chlorpromazine
Bronchodilators	Ipratropium, albuterol
Decongestants	Pseudoephedrine
Diuretics	Spironolactone, furosemide
Muscle relaxants	Baclofen
Narcotic analgesics	Meperidine, morphine
Sedatives	Flurazepam
Antihyperptensive	Prazosin hydrocloride
Antiarthritic	Piroxicam

Physiologically, the greatest salivary secretion takes place during tooth eruption and is linked to hyperstimulation of the peripheral receptors in the oral mucus. Hyperstimulation of salivary secretion also takes place during the first half of pregnancy and during menstruation, as well as resulting from smell and mechanical stimuli such as mastication and taste stimuli such as sourness and sweetness. The pathological causes of hypersalivation include those of oral origin such as the first stages of wearing dentures, dental pain or any irritation or inflammatory process in the oral-pharyngeal or digestive regions, particularly in the upper tract. Certain neurological disorders such as Parkinson's disease, epilepsy, encephalitis or some tumours can cause hypersalivation, as can exogenous poisoning by lead, bismuth, mercury, silver, gold or arsenic and endointoxications such as uremia, certain medicines such as pilocarpin, cholinesterase inhibitors, cholinergic agonists, lithium, iodides, mercury compounds or L-dopa, hyperparathyroidism and some stages of serious infectious processes; it is also associated with Riley-Day syndrome (6).

THE RÔLE OF SALIVA IN CARIES PROTECTION

The part that saliva plays in protecting against caries can be summarised under four aspects: diluting and eliminating sugars and other substances, buffer capacity, balancing demineralisation / remineralisation and antimicrobial action.

- Diluting and eliminating sugars and other substances

One of the most important functions of saliva is to remove microorganisms and dietary components from the mouth. Studies have established that following the ingestion of carbohydrates, the concentration of sugars in the saliva rises exponentially, very quickly at first and then more slowly. Dawes (11) established a sugar clearance model based on the knowledge of two factors: unstimulated salivary flow and the volume of saliva before and after swallowing the food. According to studies based on this model, clearance was faster when both salivary volumes were low and the unstimulated flow was high. After ingesting sugars, the mouth contains a small volume of saliva, around 0.8 ml. The sugar is diluted in this small quantity of saliva, where it reaches a high concentration. This stimulates the secretory response of the salivary glands, causing an increase in flow, which can reach 1.1 ml. When the food is swallowed, some sugar remains in the mouth. It is gradually diluted, thanks to the saliva being secreted, and the volume of saliva in the mouth then returns to its normal level. Consequently, a high volume of saliva at rest increases the speed of sugar removal, explaining the increased risk of caries in patients with a low unstimulated salivary flow rate. The capacity to clear sugars from the mouth remains constant over time as long as unstimulated salivary flow rates are maintained, but is drastically reduced when these are diminished. Additionally, elimination does not occur equally in all areas of the mouth. It is faster in the areas that are closest to the places where the salivary gland ducts drain into the mouth, as saliva

© Medicina Oral S.L. Email: medicina@medicinaoral.com

circulates faster there than in areas where it forms a pool. Again, the speed of clearance from the mucosa and teeth varies considerably (0.8 to 8 mm/min); even on the teeth, clearance will be slower from the surfaces that are more retentive and more difficult for the saliva to reach.

The sugars in the saliva easily spread to the bacterial plaque. A few minutes after sugar ingestion, the plaque is already supersaturated with greater concentrations than are found in the saliva; there is a correlation between pH changes in the plaque and sugar clearance from the saliva. These changes in pH and the ability of the pH to recover are expressed by Stephan's curve. pH recovery is not the same on all tooth surfaces: it presents greater difficulties in the mid-interproximal areas, which are more difficult for the saliva to reach, resulting in less dilution and a lower buffer effect against the acids in the plaque (12).

- Buffer capacity

Although saliva as such plays a part in reducing the acids in the plaque, it also contains specific buffer mechanisms such as bicarbonate, phosphate and some protein systems which not only have a buffer effect but also provide ideal conditions for automatically eliminating certain bacterial components that require a very low pH to survive. The carbonic acid – bicarbonate buffer acts above all when the stimulated salivary flow rate rises. The phosphate buffer plays an essential rôle when salivary flow is low. At a pH greater than 6 the saliva is supersaturated with phosphate with regard to hydroxyapatite (HA). When the pH falls below the critical level (5.5) the HA begins to dissolve, freeing phosphates that attempt to restore the pH balance. In the final analysis, this depends on the phosphate and calcium ion content of the surrounding medium. Certain proteins, such as histatins or sialin, as well as certain alkaline products generated by the metabolic activity of bacteria on amino acids, peptides, proteins and urea, are also important for controlling the pH of the saliva (2).

As in the case of sugar removal, the buffer mechanisms do not act equally on all the tooth surfaces. Their effect is greater on the free surfaces, which are covered by a thin layer of bacterial plaque, than on interproximal surfaces.

The mouth is often exposed to foods that have a far lower pH than that of saliva and can start to dissolve the enamel (chemical erosion). Under these conditions also, the buffer mechanisms come into action to normalise the pH as fast as possible (1).

- Balance between demineralisation and remineralisation

Caries lesions are characterised by a sub-surface demineralisation of the enamel that is covered by a fairly well mineralised layer, unlike chemical erosion, where the outer surface of the enamel is demineralised but there is no sub-surface lesion. The factors that regulate the hydroxyapatite (HA) balance are the pH and the concentration of free calcium, phosphate and fluoride ions. Both the saliva and the plaque (particularly the extracellular plaque that is in close contact with the tooth) are supersaturated with calcium, phosphate and hydroxyl ions with regard to HA. Additionally, in those who ensure an adequate intake of fluorides, particularly by using fluoridated toothpaste, both the saliva and the plaque contain abundant quantities of this ion. Also, some proteins are able to bind to the HA and inhibit the spontaneous precipitation of calcium and phosphate, thus maintaining the integrity of the enamel crystals. Proline-rich proteins, statherins, histatins and cystatins act in this way, while the action of some bacterial proteases and of salivary callicrein affects this regulatory process(13).

The caries process begins when bacteria ferment carbohydrates, resulting in the production of organic acids that lower the pH of the saliva and the plaque. In the dynamic balance of the caries process, supersaturation of the saliva provides a barrier to demineralisation and tips the balance towards remineralisation. The presence of fluoride assists this balance.

Calcium is found in greater quantities in unstimulated than in stimulated saliva as its main source is the saliva secreted by the submaxillary and sublingual glands, whereas when stimulation occurs, it is the parotid gland which produces the greatest volume of secretion. The phosphate concentration in saliva from the submaxillary glands is approximately 1/3 of that in parotid saliva but is six times higher than that of the saliva produced by the minor salivary glands (2).

- Antimicrobial action

Saliva plays an important rôle in maintaining the equilibrium of the oral ecosystems. This is essential for dental caries control. The saliva is able to perform its function of maintaining the oral microbiota balance because it contains certain proteins. These are essential constituents of the acquired pellicle, encourage bacterial aggregation, are a source of food for certain bacteria and possess an antimicrobial effect because some of them are capable of modifying the bacteria's metabolism and ability to adhere to the surface of the tooth.

The most important proteins involved in oral ecosystem maintenance are proline-rich proteins, lysozyme, lactoferrin, peroxidases, agglutinins and histidine, as well as secretory immunoglobulin A and immunoglobulins G and M (14).

THE RÔLE OF SALIVA IN BACTERIAL PLAQUE FORMATION

Bacterial plaque is a biofilm that covers all the oral structures. It is partly cellular, fundamentally bacterial, and partly acellular, from bacterial, salivary and dietary sources. It appears as a yellowish-white deposit which adheres strongly to the tooth and is not dislodged by chewing or jets of air or water, unlike the materia alba, which is composed of food debris, desquamated cells, leucocytes and unadhered bacteria and can be flushed away by a jet of water.

The first stage in bacterial plaque formation is the formation of the acquired pellicle, which takes place only a few minutes after the teeth have been well brushed. The acquired pellicle is an acellular coating, between 2 and 10 µm thick, made up of salivary proteins and other macromolecules. It provides the basis for initial colonisation by microorganisms

© Medicina Oral S.L. Email: medicina@medicinaoral.com

which, under certain conditions, form the dental plaque. However, the acquired pellicle also provides an important protection against attrition and abrasion and acts as a diffusion barrier, as it carries a negative electric charge (15). Primary bacterial colonisation takes place through specific, irreversible adhesion between the acquired pellicle receptors and the bacterial molecules known as adhesins. Proline-rich proteins are an important part of this process, as their amino-terminal segment adheres to the tooth, leaving the carboxy-terminal region free to bind to the bacteria. This stage lasts between 4 and 24 hours, with a predominance of aerobic bacteria. Secondary colonisation can last from 1 to 14 days, after which the bacteria multiply actively by aggregation and coaggregation, although some bacteria may also employ adhesion. The plaque thickness increases and anaerobic microorganisms begin to predominate in the deeper layers. Bacterial competition is established and nutrients are obtained from the breakdown of the acellular matrix and the excretion of certain bacterial metabolites that can be used as nutrients by other species.

Approximately two weeks later the mature plaque forms. Oxygen and nutrients are scarce in its deeper areas and the accumulation of waste products increases. Although this places the number of viable cells at risk, the composition of the plaque maintains a certain stability. The mature plaque may mineralise and form calculus, which has a similar microbial composition but may have a lower number of viable cells. A prerrequisite for calculus formation is that the plaque must have a more alkaline pH than the surrounding saliva or crevicular fluid. This may be the result of high proteolytic activity. Protease activity in the saliva is closely linked to calculus indices and high concentrations of urea in the plaque encourage deposition of calcium and phosphorus on the plaque. Further processes such as those described may be repeated on the calcified plaque, increasing its thickness (16).

DIAGNOSTIC APPLICATIONS OF SALIVA

Several pathways, both intra- and extracellular, enable the saliva to be reached by some substances that are not among its normal components. The most common intracellular pathways are passive diffusion and active transport. Ultrafiltration through the tight cell junctions is the best-known extracellular mechanism. Some molecules may enter the saliva from the serum by passing through the capillary barrier, the interstitial spaces and the membranes of the acinar and ductal cells until they reach the excretory tubules. Serum components may also reach the saliva through the crevicular fluid. This raises the prospect of using saliva in the diagnosis of certain pathologies (17).

The use of saliva in diagnosing caries risk is well-known, particularly in monitoring chemical treatments to control the disease (18), owing to the possibility of detecting the presence of *S. mutans* and *Lactobacillus* spp, as well as lactic acid, which causes the sub-surface demineralisation that causes the onset of the caries lesion (19). Other infectious diseases of the oral cavity can be diagnosed in this way, such as candidiasis through the presence of *Candida* spp in the saliva. The presence of periodontal pathogenic bacteria can also be diagnosed by this method. This is important, not only because it makes it possible to identify the most specifically pathogenic periodontal microflora, but also because of the potential rôle that some of these bacteria play in increasing the risk of cardiovascular and cerebrovascular diseases (20), preterm birth and low birth weight.

Cystic fibrosis, a hereditary disease which is considered an exocrinopathy characterised by an alteration in electrolyte transport in the epithelial cells and the secretion of viscous mucus by the glands and epithelia, is linked to raised sodium, chloride, calcium, phosphate, lipid and protein contents in the submaxillary saliva. An epidermal growth factor with low biological activity compared to that of healthy persons and raised prostaglandin E_2 levels are also found in the saliva of these patients (21).

For diagnosing caeliac disease, IgA and antigliadin antibody detection in saliva shows high specificity and low sensitivity, whereas their determination in serum is highly sensitive and less specific (22).

In 21-hydroxylase deficiency, a strong correlation has been found between 17-hydroxyprogesterone levels in saliva and in serum.

In Sjögren's syndrome, minor salivary gland biopsy is an accepted diagnostic procedure. A predominant inflammatory infiltrate composed of CD^4 lymphocytes is found, together with lowered at rest and stimulated salivary flow rates. Quantitatively, there are raised concentrations of sodium, chloride, IgA, IgG, lactoferrin, albumin, â2 microglobulin, cystatin C and S, lipids and inflammation mediators such as prostaglandin E_2, thromboxane B2 and interleukin-6. IgA, IgG and IgM autoantibodies can also be detected in the saliva (23).

In some malignant diseases, markers can be detected in the saliva, such as the presence of protein p53 antibodies in patients with oral squamous cell carcinoma, or high levels of defensin-1 positively correlated with the serum levels. The presence of the c-erbB-2 tumour marker in the saliva and blood serum of breast cancer patients and its absence in healthy women is a promising tool for the early detection of this disease. In ovarian cancer too, the CA 125 marker can be detected in the saliva with greater specificity and less sensitivity than in serum (24).

PCR detection of *Helicobacter pylori* in the saliva shows high sensitivity; studies have demonstrated that the oral-oral transmission route for this bacterium may be of considerable importance in developed countries (25). The presence of antibodies to other infectious organisms such as *Borrelia burdogferi*, *Shigella* or *Tenia Solium* can also be detected through the saliva.

As regards certain viral diseases, detection of hepatitis A antigen and hepatitis B surface antigen in the saliva has been used in epidemiological studies, as has that of IgM and IgG type antibodies to both types of hepatitis. There

© Medicina Oral S.L. Email: medicina@medicinaoral.com

are commercial kits for determining antibodies to hepatitis B and C viruses that are 100% sensitive and specific (26) and saliva has also been used to detect antibodies to the rubella, parotitis and rubeola viruses. In neonates, the presence of IgA is an excellent marker of rotavirus infection. Some studies have suggested that reactivation of herpes virus type 1 infections is related to the pathogenesis of Bell's palsy and that PCR detection of the virus in the saliva would be a suitable method for early detection of reactivations of this illness (27). HIV antibody detection is as precise in saliva as in serum and is applicable in both clinical and epidemiological studies. The presence of HIV virus antibodies and viral components in the saliva can assist in the diagnosis of acute infection, congenital infection and reactivations of the infection (28).

The determination of certain drugs in saliva depends on their concentration in the blood and their diffusion capacity, liposolubility and molecular size. Saliva has been used to monitor the levels of lithium, carbamazepine, barbiturates, benzodiazepines, phenytoin, theophylline and cyclosporine. Equally, there is a high correlation between ethanol concentrations in saliva and in serum. The presence of thiocyanate in the saliva is an excellent indicator of active or passive smoking. Other drugs such as cocaine or opiates can also be detected in saliva (29).

Detection in the saliva of certain hormones such as cortisol, aldosterone, testosterone, estradiol or insulin is highly correlated with concentrations in serum. Generally speaking, it is the liposoluble hormones with lower molecular weights that can be detected most reliably in the saliva, which they enter by ultrafiltration or passive diffusion, whereas protein-bound hormones will not be found as there is no active transport into the saliva (30)

Consequently, the use of saliva as an alternative method of diagnosis or as a means to monitor the evolution of certain illnesses or the dosage of certain medicines is a promising path. Its attractions for diagnosis are increased by the commercial availability of an easily used test; the accessibility of saliva and the non-invasive manner of obtaining the specimen are further advantages of using saliva as a diagnostic tool.

REFERENCES

1. Tenovuo JO. Salivary parameters of relevance for assesSing caries activity in individuals and populations. Comm Dent Oral Epidemiol 1997;25:82-6.
2. Nauntofte B, Tenevuo JO, Lagerlöf F. Secretion and composition of saliva. In: Fejerskov O and Kidd E, eds. Dental Caries. The disease and its clinical management. Oxford. Blackwell Munksgard; 2003. p. 7-29.
3. Hofman LF. Human saliva as a diagnostic specimen. J Nutr 2001;131:1621S-25S.
4. Sreebny L, Baum B, Edgar W, Epstein J, Fox P, Larmas M. Saliva: Its role in health and diseases. Int Dent J 1992; 42:291-304.
5. Ship JA. Diagnosing, managing and preventing salivary gland disorders. Oral Diseases 2002;8:77-89.
6. Meningaud JP, Pitak-Arnnop P, Chikhani L, Bertrand JC. Drooling of saliva: a review of the etiology and management options. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:48-57.
7. Dodds MW, Jonson DA, Yeh CK. Health benefits of saliva: a review. J Dent 2005;33:223-33.
8. Cohen-Brown G, Ship JA. Diagnosis and treatment of salivary gland disorders. Quintessence Int 2004;35:108-23.
9. Andrews N, Griffiths C. Dental complications of head and neck radiotherapy: part 2. Aus Dent J 2001;46:174-82.
10. Mariette X. Treatment of oral dryness in Sjogren's syndrome. Rev Med Interne 2004;25:287-93.
11. Dawes C. A mathematical model of salivary clearance of sugar from the oral cavity. Caries Res 1983;17:321-34.
12. Axelson P. Internal modifying factors in dental caries. En: Axelson P, ed. Diagnosis and caries risk prediction of dental caries vol 2. Chicago. Quintessence Publishing, 2000. p. 91-150.
13. Seif TR. Saliva su rol en la salud y en la enfermedad. En: Seif T, ed. Cariología. Prevención, diagnóstico y tratamiento de la caries dental. Caracas. Actualidades Médico odontológicas Latinoamericanas, 1997. p. 217-40.
14. Liébana J, González MP, Liébana MJ, Parra L. Composición y ecología de la microbiota oral. En: LíébanaJ, ed. Microbilogía oral . 2ª ed. Madrid. MacGraw-Hill-Interamericana, 2002. p. 515-25.
15. Bernimoulin JP. Recent concepts in plaque formation. J Clin Periodontol 2003;30:7-9.
16. Sbordone L, Bortolaia C. Oral microbial biofilms and plaque-related diseases: microbial communities and their role in the shift from oral helth to disease. Clin Oral Investig 2003;7:181-8.
17. Haeckel R, Hanecke P. Application of saliva, sweat and tear fluid for diagnostic purposes. Ann Biol Clin 1993; 51:903-10.
18. Llena MC, Bagan JV. Clorhexidne varnish application and fluoride self-administration for dental caries control in head and neck irradiated patients. A three year follow-up. Oral Biosci Med 2004;1:187-93.
19. Llena MC, Almerich JM, Forner L. Determinación de ácido láctico en el dorso de la lengua. Su relación con la presencia de caries activa. RECOE 2004;9:303-7.
20. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. J Cardiovascular Risk 1999;6:7-11.
21. Slomiany BL, Aono M, Murty VL, Slomiany A, Levine MJ, Tabaka LA. Lipid compositition of submandibular saliva from normal and cystic fibrosis individuals. J Dent Res 1982;61:1163-6.
22. Rujner J, Socha J, Barra E, Gregorek H, Madalinski K, Wozniewicz B, et al. Serum and salivary antigliadin antibodies and serum Ig A antiendomysium antibodies as a screening test for coeliac disease. Acta Pediatr 1996; 85:814-7.
23. Tishler M, Yaron I, Shiraiz I, Levartovsky D, Yaron M. Salivary and serum soluble interleukina-2 receptor in primary Sjögren syndrome. Arch Oarl Biol 1999;44:305-8.
24. Streckfus C, Bigler L, Tucci M, Thigpen JT. A preliminary study og CA15-3, c-erbβ-2, epidermal growth factor receptor, cathepsin-D, and p53 in saliva among women with breast carcinoma. Cancer Invest 2000;18:101-9.
25. Loeb MB, Riddell RH, James C, Hunt R, Smaill FM. Evaluation of salivary antibodies to detect infection with Helicobacter pylori. Can J Gastroenterol 1997;11:437-40.
26. El-Medany OM, El-Din Abdel Wahab KS, Abu Shady EA, Gad El-

© Medicina Oral S.L. Email: medicina@medicinaoral.com

Hak N. Chronic liver disease and hepatitis C virus in Egyptian patients. Hepatogastroenterology 1999; 46:1895-903.
27. Furuta Y, Fukuda S, Chida E, Takasu T, Ohtania F, Inuyama Y, et al. Reactivation of herpes simples virus type I in patients with Bell´s palsy. J Med Virol 1998;54:162-6.
28. Emmons WW. Accuracy of oral specimen testing for human immunodeficiency virus. Am J Med 1997;102:15-20.
29. Navazesh M, Denny P, Sobel S. Saliva: A fountain of opportunity. J Calif Dent Assoc 2002;30:783-8.
30. Kaufman E, Lamster IB. The diagnostic applications of saliva. A review. Crit Rev Oral Biol. Med 2002;13:197-212.

© Medicina Oral S.L. Email: medicina@medicinaoral.com