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Review

# Dysbiosis as a determinant factor of systemic and oral pathology: Importance of micorbiome☆

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ABSTRACT

Advances in genetic and epigenetic studies modified some concepts of health and disease that had been kept intact for decades. In this respect, in the last few years, microorganisms that have evolved with superior life forms for millions of years have taken an increased prominence. The genes of organisms and their microbiota constitute a microbiome that intervenes in health maintenance. The oral cavity is inhabited by a variety of microorganisms, their control aids in stabilizing oral and systemic disease. The objective of this article is to update some concepts related to oral microbiome and its correlation with general and oral health.


**Disbiosis como factor determinante de enfermedad oral y sistémica: importancia del microbioma**

*Palabras clave:*
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RESUMEN

Los avances en los estudios de genética y epigenética modifican algunos conceptos de salud y enfermedad que se habían mantenido intactos durante décadas. En este sentido, en los últimos años se está otorgando un protagonismo creciente a microorganismos que han acompañado durante millones de años de evolución a los seres vivos superiores. Los genes de estos y de su microbiota constituyen un microbioma que interviene en el mantenimiento de la salud. La boca es lugar de asiento de gran variedad de microorganismos, cuyo control ayuda a estabilizar la enfermedad oral y sistémica. El objetivo del presente artículo es actualizar algunos conceptos relativos al microbioma oral y de su vinculación con la salud oral y general.


## Introduction

Some paradigms about health and disease are changing in relation to genetics and epigenetics. Thus, the study of the conjunction of the human genome with that of the resident microbiota (microbiome) is on the increase.[1] Analysis of the microbiome helps to understand the interaction between expression and functions of our own genes and those of other organisms, especially bacteria. This article reviews the current state of knowledge regarding the microbiome and discusses important implications for oral and general health.

For millions of years, our microbiome has co-evolved with us, playing a significant role in our pathophysiology. There is evidence that resident microbes have been performing metabolic functions in animals for at least 500 million years. Genetic material from the microbes has accompanied humans on their migrations ever since their birthplace in Africa and has been used along with human markers to track migratory routes around the globe. As an example, the monitoring of *Helicobacter pylori* distinguishes populations more accurately than human genetic markers.[2,3]

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**Table 1**
Main functional contributions attributed to human microbiome.

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|---|
| Maintenance of skin barrier and mucosal function |
| Food digestion and nutrition |
| Energy and vitamin production |
| Metabolic regulation and control of fat storage |
| Processing and detoxification of environmental chemicals |
| Differentiation and maturation of the host's mucosa and immune system |
| Development and regulation of immunity, contributing to the balance between proinflammatory and anti-inflammatory processes |
| Prevention of invasion and growth of disease-promoting microorganisms (resistance to colonization) |
| Contribution to the development and maturation of the nervous system |

On the other hand, the set of relationships and tissue organization during the development conforms its epigenetic make-up. It is a key area of research, combining genetic and environmental aspects oriented towards complex biological systems.[4] The environment has continuously shaped the composition of our microbiome; from the Neolithic period, through the Industrial Revolution and into modern times. The discovery of fire, the invention of agriculture, increasing access to processed foods, exposure to heavy metals, biocides, disinfectants and antibiotics have all contributed to changes in the composition of the human microbiome.[2,5] The introduction of refined flours and sugars in our diet has contributed to certain bacteria genetically altering their metabolism. So, *Streptococcus mutans* successfully competes against other oral bacterial species by increasing its defences against oxidative stress and its resistance to the acid metabolites present in new carbohydrates. After this adaptation, its prevalence in the oral cavity increases, along with that of other acid-tolerant species.[6]

Endogenous human microbial communities participate in multiple metabolic, physiological and immunological functions (Table 1), hence any alteration in the function and composition of the microbiome can have significant health consequences.[7,8]

Our microbiome is distributed across the different compartments of the body and is very diverse and variable within and between individuals. The greatest diversity corresponds to the gastrointestinal tract and mouth. The relationship between the microbiome and the host is dynamic and is influenced by many aspects of the modern lifestyle, which can unbalance the ecosystem. Different habitats in the oral cavity support heterogeneous microbial communities, linked to oral and general health. To maintain a healthy state and prevent disease, it is necessary to consider the host and his/her residents as a whole.[1,2,9]

## Characteristics of the oral microbiome

The mouth houses the second most diverse microbial community of the body (after the intestine), with more than 700 species of bacteria. When the unstable balance of the oral ecosystem is broken, dysbiosis occurs. This allows bacteria that promote disease to manifest and cause disease, such as tooth decay, gingivitis and periodontitis, which have an impact on general health.[2] Bacterial colonization begins at birth. The acquisition of the microbiota (natural or caesarean delivery) and feeding (natural or artificial breastfeeding) influence the subsequent diversity of the oral and systemic microbiome.[10,11] At 3 months of age, breastfeeding offers a greater oral lactobacilli colonization than artificial milk. The eruption of teeth provides new surfaces for microbial colonization and constitutes an important ecological event in the infant's mouth. Later, the replacement of the primary teeth by the definitive teething again significantly modifies the oral microbial habitat.[2,12]

The colonization of the oral medium is favoured by the presence of a thin mucilaginous layer, called acquired pellicle. This layer consists of proteins, lipids and other components (carbohydrates, nucleic acids), mainly derived from saliva, but also derived from the crevicular fluid (gingival sulcus), oral mucosa and bacteria. This film modulates the binding of bacteria to dental and epithelial surfaces and protects the mucosa.[13] The individual composition of the acquired pellicle favours bacterial adhesion, with which it interacts. The colonized surface constitutes a *biofilm* or plaque of biological activity. Saliva contributes to the maintenance and control of the *biofilm* and modulates bacterial plaque layers, involving numerous proteins and minerals such as secretory immunoglobulin A, lactoferrin, lactoperoxidase, lysozyme, staterin and histatins. Saliva and crevicular fluid provide nutrients for microbial growth and contain components with antimicrobial activity.[14,15]

Collaboration and antagonism among the *biofilm* species contribute to the ecological stability, have an impact on the virulence and pathogenic potential of bacteria and are involved in tolerance to host defences and antimicrobial agents.[16] Several microbial colonization habitats are recognized in the mouth, such as teeth, gingival sulcus, gum, tongue, cheek, lips and palate. They constitute a very heterogeneous ecological system and favour the growth of different microbial communities on the previously mentioned acquired pellicle.[17] Resident bacteria have pro and anti-inflammatory activities, essential for maintaining homeostasis in the oral cavity.[18] Acute infections of the oral mucosa are quite rare, despite dense microbial colonization.[19] They are attributed to host–microbe interactions, the importance of which is highlighted by immunocompromised patients who may experience life-threatening bacterial, viral and fungal infections.[2]

The promotion of hygienic measures at the end of the XIX century in the developed world (brushing, flossing)[20] has contributed to a change in oral microbiome composition.[21] Likewise, the consumption of sugary drinks and refined sugars or smoking has probably had an additional impact on the oral ecosystem,[22] causing conditions such as caries and periodontal disease and favouring the growth of certain microorganisms in the *biofilm*, with unpleasant organoleptic repercussions, such as bad breath.[23,24]

## Systemic repercussions

The oral microbiota also intervenes in systemic processes. An example is the effect of oral bacteria expressing nitrate reductase, which catalyze the conversion of dietary nitrates into nitrites. When swallowed, salivary nitrite is transformed into nitric oxide, a potent vasodilator with antimicrobial activity, which plays an important role in the maintenance of cardiovascular health. Nitrite also stimulates the production of gastric mucus. Moderate nitrate consumption lowers blood pressure, inhibits platelet function and improves endothelial function; the sustained intake of nitrates in the diet improves vascular function in patients with hypercholesterolemia. These improvements are associated with changes in the oral microbiome in favour of organisms that are able to reduce nitrites.[2,25] However, while dietary nitrates increase nitrite formation, nitric oxide in tissues interacts with superoxide radicals released by immune cells, forming peroxynitrite anions, with cell damage. Several small-scale studies have apparently shown that the use of mouthwashes containing chlorhexidine can reduce nitrite concentration in both saliva and plasma, contributing to blood pressure control. The issue of nitrate/nitrite/nitric oxide effects on health is still controversial, which is why these interesting data require confirmation with larger scale studies that provide solid conclusions.[2,26,27]

The relationship between oral pathogens and systemic effects has been demonstrated in animals, where oral administration of *Porphyromonas gingivalis* changed the composition of the intestinal microbiome, triggering inflammatory processes in diverse tissues and organs.[28] Oral bacteria play a role in various systemic conditions, including cardiovascular disease, rheumatoid arthritis, adverse effects on pregnancy, stroke, inflammatory bowel disease and colorectal cancer, respiratory tract infections, meningitis or brain abscesses, abscesses in the lungs, liver and spleen, appendicitis, pneumonia and diabetes.[17,24,29–34] Advanced periodontitis interferes with glycaemic control in diabetes and in subjects who do not suffer from it. Also, advanced periodontitis is associated with an increased risk of type 2 diabetes and, in diabetic patients, there is a direct correlation between the severity of periodontitis and the complications of the disease. In recent years, increased interest has been shown in clarifying the possible relationship between periodontal diseases and certain systemic processes, such as ischaemic cardiovascular events, premature births and/or infants with low birth weight, obesity, diabetes mellitus, pulmonary infections, etc.[30] All these chronic inflammatory processes have a link with periodontitis, which has motivated the current interest in the concept of periodontal medicine.[35] This fact is relevant, since non-notifiable chronic diseases (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes) are the leading cause of death and disability worldwide and causes more deaths now than all other diseases combined in the developed world.[36]

The alteration of the microbiome has been linked to: 1) exposure to disturbing molecules (food ingredients like sugars, gluten, chlorinated water, antibiotics, a variety of chemicals); 2) shortage of nutrients that promote healthy colonies of bacteria (vegetable-deficient diets with fibre or with excessive saturated fats), and 3) situations that promote and maintain stress. Consequently, the altered microbiome contributes to a state of chronic inflammation that predisposes to diseases as diverse as asthma, various allergies, obesity, diabetes, cancer, depression, autism, arthritis, ischaemic heart disease, multiple sclerosis, Parkinson's disease and Alzheimer's disease.[2] Microbial alteration and chronic inflammatory processes favour mucosal permeability of the different tracts involved (eyes, nose, mouth, throat, respiratory tract, gastrointestinal tract, urogenital tract), which are broad pathways for potential pathogens. The current lines of research, in relation to these aspects, are changing many classic diagnostic and therapeutic concepts.[2,37,38]

## Discussion

When the species of microorganisms that reside in the oral cavity or other body surfaces remain in balance (symbiosis), we refer to it as a healthy state. On the contrary, the rupture of this balance (dysbiosis) is associated with disease and is characterized by the alteration of the diversity and the relative proportions of microbiota species.[39] The relationship between oral microbiome and its host is a dynamic one. The composition of microbial colonies in healthy mouths is usually very stable, but biological changes in a person's life can influence the species balance within these colonies.[40] Healthy individuals often adapt to age-specific physiological changes or hormonal changes regarding puberty and pregnancy without detriment to their oral health.[41] In other situations, disturbance of the oral ecosystem may lead to dysbiosis and loss of balance or diversity in the *biofilm's* community, predominating a single or a few species and increasing the associated risk of disease.[42] Salivary gland dysfunction (changes in saliva flow and/or composition), poor oral hygiene, gingivitis and lifestyles, including eating and toxic habits (such as smoking or chewing tobacco, alone or associated with other substances) as well as certain sexual behaviours are predisposing factors to oral dysbiosis.[11,43–46] It is now considered that bacteria labelled as oral pathogens can be found in a small number in healthy sites and that oral disease occurs because of a deleterious change in the natural balance of the microbiota rather than as a result of an exogenous "infection".[40] The dysbiosis of periodontal disease, as a cause of bacteraemia, probably favours the systemic spread of oral bacteria. Therefore, good oral hygiene will be required to control the total bacterial load.[24]

As a way of combating bacterial dysbiosis, many authors propose the administration of probiotics (contain strains of bacteria and/or beneficial yeasts) and prebiotics (foods rich in fibre) to regulate microbiome balance. Faecal transplants (from healthy bacterial communities) are also being promoted in some countries, apparently with increasing success in the treatment and prevention of various systemic diseases.[47–49]

These non-invasive treatments may compensate for the indiscriminate use of antibiotics, but the variety and number of species to be transplanted in this way are limited and may not be sustainable. For this reason, they should be accompanied by a balanced diet and the intake of prebiotics.[50] The Mediterranean diet seems to be a good model to promote. On the other hand, organic foods (of animal or vegetable origin), less processed and less manipulated during their production, offer greater guarantees of respecting the microbiome than those handled genetically or with chemicals (agrochemicals, antibiotics, hormones, etc.). On the other hand, the intake of liquids is a priority. Essential to survival, water is a vehicle for various elements and mineral salts. The chlorination of water may negatively influence the homeostasis of the microbiome, so it should be a factor to consider.[51] In short, measures such as those summarized in Table 2 are recommended to prevent and combat dysbiosis.

Although the interaction of the bacterial microbiota with the human genome has been discussed in previous paragraphs, the coevolutionary process of the human microbiome has involved other microorganisms, carriers of their respective genetic load, such as unicellular fungi (yeasts), protozoa and viruses. All of them have been integrating and evolving, forming part of ecological niches (skin, mouth, digestive system, respiratory system, genital apparatus) and maintaining a balanced relationship between them. The technological advances that have taken place in the last century, plus advances in other areas (such as lifestyles, food, hygiene, toxic habits, drugs, pesticides, etc.), especially in the Western world, have contributed to a significant change in the microbiome, without time to adapt. Hence the higher rates of certain forms of disease, more prevalent in the so-called civilized world.

An essential role can be attributed to viruses. Even though they are not considered living beings, they can clearly act on the genome.[52,53] They are nanoparticles that behave like intracellular parasites. They parasite all types of cells, including bacteria (bacteriophages), inducing the formation and dissemination of their genetic information by different mechanisms and have been doing so since life began on this planet (perhaps with a leading role in the evolutionary process).[54] Certain diseases, such as the autoimmune disease, may be due to dysbiotic processes in which particles such as viruses act by modifying some proteins. Their action could justify integumentary reactive patterns, such as lichenoid or pemphigoid manifestations, or aphthous ulcerative systemic disorders,

**Table 2**
Recommended measures to reduce dysbiotic processes.

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|---|
| Regular oral hygiene (to keep the mouth's microbiota under control) |
| Healthy diet (with abundant vegetables and few foods with flours and refined sugars) |
| Maintain an adequate BMI (to avoid metabolic syndrome), monitoring weight, blood pressure and doing aerobic exercise on a regular basis |
| Avoid saturated and hydrogenated fats, giving priority to monounsaturated fatty acids (olive oil) and omega-3 polyunsaturates (more than omega-6) |
| Avoid the indiscriminate and unjustified administration of antibiotics as well as the intake of meat from animals that have been treated with antibiotics or with hormones |
| Restrict as far as possible cosmetic products or foods containing molecules of dubious efficacy or recognized toxicity (endocrine disruptors) |

such as Crohn's disease, ulcerative colitis or Behçet's disease. It is unclear whether these nosological entities are disorders in themselves or rather inflammatory manifestations, involving an altered microbiome.[55–57] The action of viruses on the genetic material (RNA, DNA) can modify the expression of protooncogenes and oncogenes, facilitating the development of cancer.[58,59] The use of virus-like particles in nanomedicine helps with detection, prevention (vaccination), diagnosis and improvement of the treatment of diseases such as cancer or cardiovascular disease. In all probability, this will also be a line of research to be promoted in the near future.[60]

To conclude, it is evident that oral and systemic microbiome are closely related and that its alteration (dysbiosis) has a great impact on health. Therefore, the diagnosis and treatment of the oral condition contributes to therapeutic success and systemic disease prevention, which must be understood in a holistic way.

## Conflict of interests

The authors declare no conflict of interest.

## References

1. Methé BA, Nelson KE, Pop M, Creasy HH, Giglio MG, Huttenhower C, et al. A framework for human microbiome research. Nature. 2012;486:215–21.
2. Kilian M, Chapple ILC, Hannig M, Marsh PD, Meuric V, Pedersen AM, et al. The oral microbiome – an update for oral healthcare professionals. Br Dent J. 2016;221:657–66.
3. Rinaldi A. Tiny travel companions. As microorganisms have accompanied mankind's journeys around the globe, they could help scientists to unravel our past. EMBO Rep. 2007;8:121–5.
4. Zerón A. Genoma, microbioma y epigenoma humano. Una visión contemporánea de la tríada ecológica. Rev ADM. 2014;71:162–70.
5. Gillings M, Paulsen I, Tetu S. Ecology and evolution of the human microbiota: fire, farming and antibiotics. Genes (Basel). 2015;6:841–57.
6. Cornejo OE, Lefébure T, Bitar PD, Lang P, Richards VP, Eilertson K, et al. Evolutionary and population genomics of the cavity causing bacteria Streptococcus mutans. Mol Biol Evol. 2013;30:881–93.
7. Krajmalnik-Brown R, Ilhan ZE, Kang DW, DiBaise JK. Effects of gut microbes on nutrient absorption and energy regulation. Nutr Clin Pract. 2012;27:201–14.
8. Relman DA. The human microbiome and the future practice of medicine. JAMA. 2015;314:1127.
9. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. Science. 2009;326:1694–7.
10. Lif Holgerson P, Harnevik L, Hernell O, Tanner AC, Johansson I. Mode of birth delivery affects oral microbiota in infants. J Dent Res. 2011;90:1183–8.
11. Jesús de la Calle I, Jesús de la Calle MA. Vaginosis bacteriana. Med Clin (Barc). 2009;133:789–97.
12. Holgerson PL, Vestman NR, Claesson R, Ohman C, Domellöf M, Tanner AC, et al. Oral microbial profile discriminates breast-fed from formula-fed infants. J Pediatr Gastroenterol Nutr. 2013;56:127–36.
13. Hannig C, Hannig M, Attin T. Enzymes in the acquired enamel pellicle. Eur J Oral Sci. 2005;113:2–13.
14. Marsh PD, Do T, Beighton D, Devine DA. Influence of saliva on the oral microbiota. Periodontol 2000. 2016;70:80–92.
15. López-López J, Jané Salas E, Chimenos Küstner E. Pronóstico y tratamiento de la boca seca. Revisión sistemática. Med Clin (Barc). 2014;142:119–24.
16. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev. 2002;15:167–93.
17. Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, et al. The human oral microbiome. J Bacteriol. 2010;192:5002–17.
18. Devine DA, Marsh PD, Meade J. Modulation of host responses by oral commensal bacteria. J Oral Microbiol. 2015;7:26941.
19. Zaura E, Nicu EA, Krom BP, Keijser BJ. Acquiring and maintaining a normal oral microbiome: current perspective. Front Cell Infect Microbiol. 2014;4:85.
20. American Dental Association. History of dentistry timeline. Available from: http://www.ada.org/en/about-the-ada/ada-history-and-presidents-of-the-ada/ada-history-of-dentistry-timeline [accessed 08.05.17].
21. Marsh PD. Controlling the oral biofilm with antimicrobials. J Dent. 2010;38 Suppl. 1:S11–5.
22. Adler CJ, Dobney K, Weyrich LS, Kaidonis J, Walker AW, Haak W, et al. Sequencing ancient calcified dental plaque shows changes in oral microbiota with dietary shifts of the Neolithic and Industrial revolutions. Nat Genet. 2013;45:450–5.
23. De Luca-Monasterios F, Chimenos-Küstner E, López-López J. Efecto de masticar chicle sobre la halitosis. Med Clin (Barc). 2014;143:64–7.
24. Han YW, Wang X. Mobile microbiome: oral bacteria in extra-oral infections and inflammation. J Dent Res. 2013;92:485–91.
25. Velmurugan S, Gan JM, Rathod KS, Khambata RS, Ghosh SM, Hartley A, et al. Dietary nitrate improves vascular function in patients with hypercholesterolemia: a randomized, double-blind, placebo-controlled study. Am J Clin Nutr. 2016;103:25–38.
26. Woessner M, Smoliga JM, Tarzia B, Stabler T, van Bruggen M, Allen JD. A stepwise reduction in plasma and salivary nitrite with increasing strengths of mouthwash following a dietary nitrate load. Nitric Oxide. 2016;54:1–7.
27. Kapil V, Haydar SM, Pearl V, Lundberg JO, Weitzberg E, Ahluwalia A. Physiological role for nitrate-reducing oral bacteria in blood pressure control. Free Radic Biol Med. 2013;55:93–100.
28. Arimatsu K, Yamada H, Miyazawa H, Minagawa T, Nakajima M, Ryder MI, et al. Oral pathobiont induces systemic inflammation and metabolic changes associated with alteration of gut microbiota. Sci Rep. 2014;4:4828.
29. Pedersen AML, editor. Oral infections and general health. Cham: Springer International Publishing Switzerland; 2016., http://dx.doi.org/10.1007/978-3-319-25091-5.
30. Chapple IL, Genco R, working group 2 of the joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol. 2013;84 Suppl.: S106–12.
31. De Pablo P, Chapple IL, Buckley CD, Dietrich T. Periodontitis in systemic rheumatic diseases. Nat Rev Rheumatol. 2009;5:218–24.
32. Rodríguez de Santiago E, Albillos Martínez A, López-Sanromán A. Infecciones en la enfermedad inflamatoria intestinal. Med Clin (Barc). 2017;148:415–23.
33. Sebastián Domingo JJ. Síndrome del intestino irritable: lo (pen)último sobre lo que se está investigando. Med Clin (Barc). 2016;146:260–2.
34. Tor J, Muga R. El hígado graso y el síndrome metabólico. Med Clin (Barc). 2013;141:252–3.
35. Williams RC, Offenbacher S. Periodontal medicine: the emergence of a new branch of periodontology. Periodontol 2000. 2000;23:9–12.
36. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. IARC Monogr Eval Carcinog Risks Humans. 2004;85:1–334.
37. Szot P, Franklin A, Figlewicz DP, Beuca TP, Bullock K, Hansen K, et al. Multiple lipopolysaccharide (LPS) injections alter interleukin 6 (IL-6), IL-7, IL-10 and IL-6 and IL-7 receptor mRNA in CNS and spleen. Neuroscience. 2017;355: 9–21.
38. Gomes C, Martinho FC, Barbosa DS, Antunes LS, Póvoa HC, Baltus TH, et al. Increased root canal endotoxin levels are associated with chronic apical periodontitis, increased oxidative and nitrosative stress, major depression, severity of depression, and a lowered quality of life. Mol Neurobiol. 2017, http://dx.doi.org/10.1007/s12035-017-0545-z.
39. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. Nat Rev Genet. 2012;13:260–70.
40. Marsh PD, Head DA, Devine DA. Ecological approaches to oral biofilms: control without killing. Caries Res. 2015;49 Suppl. 1:46–54.
41. Zaura E, Ten Cate JM. Towards understanding oral health. Caries Res. 2015;49 Suppl. 1:55–61.
42. Gross EL, Leys EJ, Gasparovich SR, Firestone ND, Schwartzbaum JA, Janies DA, et al. Bacterial 16S sequence analysis of severe caries in young permanent teeth. J Clin Microbiol. 2010;48:4121–8.
43. Wu J, Peters BA, Dominianni C, Zhang Y, Pei Z, Yang L, et al. Cigarette smoking and the oral microbiome in a large study of American adults. ISME J. 2016;10:2435–46.
44. Parmar G, Sangwan P, Vashi P, Kulkarni P, Kumar S. Effect of chewing a mixture of areca nut and tobacco on periodontal tissues and oral hygiene status. J Oral Sci. 2008;50:57–62.
45. Shrinkhala S, Roopa DA, Gopal S, Johari S, Pandey Y, Gupta T. Periodontal status among gutka chewers – a prevalence study. IJIRAS. 2016;3:284–9.
46. Javed F, Vohra F, Al-Kheraif AA, Malmstrom H, Romanos GE. Comparison of periodontal inflammatory conditions among habitual gutka chewers and betel quid chewers. Oral Dis. 2015;21:437–42.
47. Hu Y, Zhou F, Yuan Y, Xu Y. Efectos del suplemento de probióticos en pacientes con diabetes mellitus tipo 2: metaanálisis de ensayos aleatorizados. Med Clin (Barc). 2017;148:362–70.
48. Borody TJ, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. Curr Gastroenterol Rep. 2013;15:337.
49. Flannigan KL, Rajbar T, Moffat A, McKenzie LS, Dicke F, Rioux K, et al. Changes in composition of the gut bacterial microbiome after fecal microbiota transplantation for recurrent *Clostridium difficile* infection in a pediatric heart transplant patient. Front Cardiovasc Med. 2017;4:17.
50. Di Bartolomeo F, Startek JB, van den Ende W. Prebiotics to fight diseases: reality or fiction? Phytother Res. 2013;27:1457–73.
51. Revetta RP, Gomez-Alvarez V, Gerke TL, Santo Domingo JW, Ashbolt NJ. Changes in bacterial composition of biofilm in a metropolitan drinking water distribution system. J Appl Microbiol. 2016;121:294–305.
52. Puy D, Chimenos-Küstner E, Dorado C. Infección bucal por el virus del herpes simple: mecanismos patogénicos conocidos. Med Clin (Barc). 1998;111: 105.
53. de Sousa Rodrigues PM, Teixeira AL, Chimenos Kustner E, Medeiros R. Are herpes virus associated to aggressive periodontitis? A review of literature. J Oral Maxillofac Pathol. 2015;19:348–55.
54. Ding ZF, Cao MJ, Zhu XS, Xu GH, Wang RL. Changes in the gut microbiome of the Chinese mitten crab (*Eriocheir sinensis*) in response to White spot syndrome virus (WSSV) infection. J Fish Dis. 2017, http://dx.doi.org/10.1111/jfd.12624.

55. Cervera Segura R, Font Franco J. Enfermedad autoinmune e infección: una relación bidireccional. Rev Clin Esp. 2003;203:167–9.
56. Schemel-Suárez M, López-López J, Chimenos-Küstner E. Oral ulcers: differential diagnosis and treatment. Med Clin (Barc). 2015;145:499–503.
57. Chimenos-Küstner E, Larred-Conde N, Marques-Soares MS, López-López J. Manifestaciones orales de toxicidad sistémica: patología liquenoide. Piel. 2015;30:644–9.
58. Jané-Salas E, Chimenos-Küstner E, López-López J, Roselló-Llabrés X. Importance of diet in the prevention of oral cancer. Med Oral. 2003;8:260–8.
59. González Svatetz CA, Goday Arnó A. Obesidad y cáncer: «las amistades peligrosas». Med Clin (Barc). 2015;145:24–30.
60. Matoba T, Koga J, Nakano K, Egashira K, Tsutsui H. Nanoparticle-mediated drug delivery system for atherosclerotic cardiovascular disease. J Cardiol. 2017, http://dx.doi.org/10.1016/j.jjcc.2017.03.005, pii:S0914-5087(17)30092-8.