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Gender differences and oral microbiota

Tindarita Todaro

Odontologist, Vibo Valentia, Italy

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Summary. After the intestinal, the oral microbiota is the richest in composition. More than 700 species contribute to its structure, reflecting the different microenvironments of the mouth. Therefore, the oral microbiota can be defined as a 'gender-specific' entity, because it is characteristic of each individual.

The gender difference is confirmed by clinical studies that show how in women during menopause the intestinal microbiota changes and the oral microbiota as well. The oral microbiota shows another face of its gender-specific nature when it comes to pregnant women.

The oral microbiota has also been implicated in some cancers with gender-specific differences, as in esophageal carcinoma and colon-rectal cancer, two tumors decidedly more common among men, or in pancreatic cancer, a tumor that particularly affects women between 34 and 55 years of age, while from 55 onwards it assumes a purely male connotation.

Keywords. Oral microbiota, gender, systemic diseases.

All the activity of our organism is kept in balance by the right relationship between the various species of microorganisms. Each species prefers specific districts, but is closely in contact with those that colonize neighboring districts. These organized groups of microorganisms make up the various 'microbiota' and they are governed by the microbiome, which constitutes their genetic source.

After the intestinal, the oral microbiota is the richest in composition. More than 700 species contribute to its structure, reflecting the different microenvironments of the mouth. The host greatly influences the composition of the oral microbiota with their habits, to the point that it can be compared to an identity card, because no two are perfectly alike. The microbiome consists of a 'core' in which species common to healthy subjects are recognized: *Streptococcus, Prevotella, Haemophilus, Rothia, Veillonella, Neisseria, Fusobacterium, Porphyromonas*. The composition is affected by lifestyle, nutrition, social status. Therefore, the microbiota can be defined as a 'gender-specific' entity, because it is characteristic of each individual. It can be preserved thanks to foods rich in fiber and dairy products and by limiting sugars and fats. The subject also interferes with the microbiota by secreting immunoglobulin A from the salivary glands and antimicrobial peptides, such as lysozyme and lactoferrin: the biofilm is thus formed. The biofilm makes the microorganisms that come together in it stronger, because they can better adhere to gum, teeth and tongue surfaces.

The oral microbiota acts as a sentinel barrier, because it is the first frontier that pathogenic microorganisms encounter when they try to reach the airways and beyond. *Streptococcus salivarius* is highly represented in the oral microbiota, and when this for some reason decreases, its locum is occupied by pathogenic microorganisms such as *Moraxella catarrhalis, Haemophilus influentiae, Streptococcus pneumoniae* and *pyogenes*. We can therefore affirm that in a situation of eubiosis (balance between the elements of the microbiota) the subject is in good health, while if one goes into dysbiosis the state of health is impaired.

In women, estrogens modulate the levels of pro-inflammatory cytokines, and therefore protect the oral cavity by modulating its microbiota. The gender difference is confirmed by clinical studies that show how during menopause, by decreasing the circulating estrogens, the intestinal microbiota changes and the oral microbiota as well. Obesity or overweight also have an influence on the microbiota.[1]

The oral microbiota shows another face of its "gender-specific" nature when it comes to pregnant women. In fact, pregnant women show a percentage increase of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in the gingival sulcus in the first trimester, while *Candida albicans* increases in the third trimester. Immediately after childbirth, there is a decrease in the presence of numerous bacterial species. All types of streptococci, *Fusobacterium nucleatum polymorphum*, *Leptotrichia buccalis, Selenomonas noxia, Veillonella parvula*, and all *Capnocytophaga* decrease.[1] The microbiota can therefore be considered dependent on gender, since the strains which are present vary in a gender-specific way.

The composition of the microbiota is also influenced by stress, hormonal alterations and physical activity. In fact, the catecholamines that are modulated during physical activity and increase during stress have been

detected in the saliva. Finally, the microbiota is affected by circadian oscillations, which determine variations in its composition.[2] Some chemicals, such as herbicide pesticides, heavy metals, plastics and the like, introduced through food, as found by laboratory experiments, alter hormonal functions, and consequently the oral microbiota. It can therefore be assumed that the microbiota is a sort of "virtual endocrine organ".[2]

The microbiota of subjects who use alcohol has more gram-positive bacteria, including *Streptococcus mutans,* while *Fusobacteria* decrease due to the presence of toxic acetaldehyde in spirits. Red wine does not create alterations.[3] Antibiotics decrease actinobacteria, and sometimes the bacterial function also changes.

The microbiota shows once again to be a gender entity also in relation to the social class involved in the analysis. This depends on the diet. More well-off people have higher levels of *Megasphaera micronuciformis*, *Veillonella atypical*, *Veillonella parvula*, *Rothia mucillaginosa*, *Prevotella histicola*, *Fusobacterium periodonticum*, *Granulicatella adiacens* and *Tannerella forsythia*, while less well-to-do people have less biodiversity: *Aggregatibacter segnis, Achromobacter xylosoxidans* and *Neisseria cluster II*.[1, 4]

When the microbiota is contaminated by pathogenic bacteria, oral conditions are established which have been proven to cause systemic disorders. The subjects affected by esophageal carcinoma, a tumor that most affects men between the ages of 50 and 60, show for 61% the presence of *Porphyromonas gingivalis* in diseased tissue and 12% in healthy tissue. This bacterium is absent in healthy subjects.[5] The same bacterium, following primary oral infection, stimulates the production of inflammatory cytokines. These in turn can interact with atheromatous plaques complicating atherosclerosis, a disease that mainly affects men. Women begin to be affected especially after menopause. More generally, cardiovascular diseases have important connections with the oral microbiota. For example, some important coronary diseases are associated with the presence in the oral microbiota of *Campylobacter rectus, Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella intermedia* and *Prevotella nigrescens*, absent in non-pathological conditions. The presence of *Actinomycetemcomitans* at the subgingival level in the periodontal disease doubles the risk of coronary arterial disease.[6]

But the oral microbiota has also been implicated in some other cancers. For example, colorectal cancer, a tumor decidedly more common among men, shows *Fusobacteria*, *Parvimonas* and *Peptostreptococcus* in the patient's microbiota. For subjects suffering from pancreatic carcinoma (a tumor that particularly affects women between 34 and 55 years of age, while from 55 onwards it assumes a purely male connotation), the risk doubles in subjects with untreated periodontitis.[7-9] Oral squamous cell carcinoma has *Porphiromonas gingivalis* as a proven risk factor and represents 3% of all male cancers and 2% of female cancers, affecting, over age 50, a 3-fold proportion of men compared to women, affecting within each gender strong smokers and consumers of alcohol.[10,11]

A relation has also been hypothesized between periodontitis and cognitive faculties and dementia. In the spinal fluid of subjects with Alzheimer's disease, we once again find *Porphyromonas gingivalis* and, in preclinical experiments, it has been suggested that COR388 – a novel, orally-administered bacterial protease inhibitor targeting gingipains produced by the periodontal pathogen *Porphyromonas gingivalis* – can inhibit the production of amino acid beta amyloid (Ab42) peptide, decreasing the inflammation of the hippocampus, that is the part of the brain associated with memory and which often undergoes degeneration already from the early stages of Alzheimer's clinical manifestations.[12]

The oral microbiota also undergoes mutations during COVID-19 infection. This was suggested by a study[13] demonstrating that in sick subjects there is a 40% decrease in the bacterial variety present in the oral cavity. Sick subjects showed a prevalence of *Prevotella* and *Veillonella*, whereas healthy subjects had a predominance of streptococci and *Rothia*. Sick patients show a large amount of local pro-inflammatory cytokines, while in subjects with a high percentage of streptococci these had low levels. Therefore, researchers suggest the development of probiotics containing biomarkers, such as streptococci and *Rothia*, to be used locally to counteract the so-called cytokine storms produced in subjects affected by COVID-19.[13]

Key messages

- The microbiota can be defined as a 'gender-specific' entity, because it is characteristic of each individual.
- The gender difference is confirmed by clinical studies that show how during menopause, by decreasing the circulating estrogens, the female intestinal microbiota changes and the female oral microbiota as well.
- The oral microbiota shows another face of its "gender-specific" nature when it comes to pregnant women, who show a percentage increase of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in the gingival sulcus in the first trimester, while *Candida albicans* increases in the third trimester.
- The oral microbiota has also been implicated in some cancers with gender-specific differences, as in esophageal carcinoma and colon-rectal cancer or in pancreatic cancer.
- The oral microbiota is very important for identifying biomarkers for local or systemic diseases, since it is easy to collect.

In conclusion, we can emphasize the fact that the oral microbiota is very important for identifying biomarkers for local or systemic diseases, since it is easy to collect. By analyzing the microbiota before treating periodontal diseases or after treating them, it could be possible not only to obtain the proof of the efficacy of the therapies but, also, to implement a robust prevention for diseases of great social impact.[14] We can conclude by suggesting that the study of the oral microbiota could provide useful information to allow medicine to reach new and unexpected goals.

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Conflict of interest statement: the Author declares no conflicts of interest.

Correspondence to:
Tindarita Todaro
email tindarita@alice.it