NUTRITIONAL INFLUENCES ON ORAL INFECTIONS: THE ORAL MICROBIOTA MODULATION

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Palavras-chave: Microbiota Oral. Cárie Dentária. Doença Periodontal. Saúde Nutricional. Probiótico. Prebiótico.

RESUMO

Introdução: A microbiota oral possui aproximadamente 700 microrganismos simbiontes responsáveis pela homeostase da saúde bucal. Contudo, alterações na microbiota oral podem gerar processos disbióticos que favorecem o agravamento de infecções como a cárie e a doença periodontal. Essas infecções orais, além do acometimento sistêmico, podem comprometer a integridade dos dentes e também da saúde bucal. Dessa forma, a alimentação inadequada mostra-se um fator de risco que influência na prevenção e no tratamento dessas infecções orais. **Objetivo**: Este estudo visa evidenciar a influência nutricional na modulação da microbiota oral afetando a longo prazo a microbiota intestinal, destacando o uso de probióticos e prebióticos no tratamento de infecções orais através de uma revisão de literatura. **Síntese de dados**: A suplementação de determinados nutrientes e a ingestão de uma dieta adequada em macronutrientes e micronutrientes influenciam diretamente no estado nutricional e consequentemente na manutenção da homeostase oral-sistêmica. Além disso, devido à multirresistência microbiana, terapias com probióticos e prebióticos têm sido adotadas como auxiliares no tratamento de infecções orais. **Conclusão**: A Odontologia Personalizada deve integrar conhecimentos multidisciplinares de atenção à saúde. Isso além de saber quando encaminhar e trabalhar junto com o Nutricionista.

Keywords: Oral Microbiota. Dental Caries Periodontal Disease. Health Nutrition. Probiotic and Prebiotic.

ABSTRACT

Introduction: The oral microbiota has approximately 700 symbiotic microorganisms responsible for oral health homeostasis. However, changes in oral microbiota can generate dysbiotic processes that favor the worsening of infections such as caries and periodontal disease. These oral infections, in addition to systemic involvement, can compromise the teeth integrity as well as oral health. Thus, inadequate nutrition proves to be a risk factor influencing the prevention and treatment of these oral infections. **Objective**: This study aims to evidence the nutritional influence on the oral microbiota modulation affecting, in the longterm, the gut microbiota, highlighting the use of probiotics and prebiotics in the treatment of oral infections by a literature review. **Synthesis of data** : Supplements of certain nutrients and the intake of an adequate diet in macronutrients and micronutrients directly influence nutritional status and consequently in the maintenance of oral-systemic homeostasis. In addition, due to microbial multidrug resistance, therapies using probiotics and prebiotics have been adopted as aids to the treatment of oral infections. **Conclusion**: Personalized Dentistry must integrate multidisciplinary knowledge of attention for health care. This in addition to knowing when to refer and work together with a Nutritionist.

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INTRODUCTION

Oral Health (OH) is governed by an extensive and diverse oral microbiota, and alterations in this composition are associated with dysbiosis process and oral infections development[1] such as Caries and Periodontal Disease (PD), which are polymicrobial and multifactorial processes that may compromise the integrity of the teeth, as well as oral and systemic health.[2] Among the risk factors for Caries and PD, malnutrition stood out as one of the most influential factors.[3]

Moreover, one of the factors that should be considered in this perspective is the Nutritional Health (NH). The NH requires the adequate supply of macronutrients and micronutrients in cells and organisms for systemic health homeostasis. Thus, there are strong associations, with many interrelating factors of NH, OH and systemic health conditions in a bidirectional relationship.[4,5]

Due to the treatment's difficulty and the antimicrobial resistance, probiotic and prebiotic nutritional therapy has been adopted as adjunctive resource to non-surgical oral infections treatment.[6] Probiotics and Prebiotics are, respectively, live microorganisms and nondigestible food components that affect beneficially the microbiota, modulating it and selectively stimulating bacterial species.[7,8] Therefore, the aim of this review is to evidence the nutritional influence on the oral microbiota modulation affecting, in the long-term, the gut microbiota, highlighting the use of probiotics and prebiotics in the treatment of oral infections.

Oral-gut microbiota interaction: the role of oral health in systemic health

The oral cavity has many sites, each one of them coated with a saliva pellicle and bacterial biofilms. Some of these bacteria have been implicated in oral diseases such as caries and periodontitis, that are among the most common bacterial infections in humans. Within the oral cavity, there are distinct microenvironments colonized by microorganisms that may have genetic and physiologically evolved to tolerate it.[9] A successful bacterium is the one who survived the harmful environment in the oral cavity and that specifically adhered to a surface. More than 700 species were detected in the oral cavity, however almost 50% are uncultivable species. They are constantly making interactions, including substrate supply for site attachment and colonization, nutritional cross feeding, and the coordinated metabolism of complex substrates, sustaining the polymicrobial synergy concept.[2]

The Gastrointestinal Tract (GI tract) is the most densely colonized human organ, it harbors complex microorganisms' communities residing in or passing through the GI tract.[10,11] These microorganisms form complex interactions in the GI tract and their communities contain approximately 500-1,000 species. These species, interestingly, belong to only few numbers of bacterial phyla: Firmicutes, Bacteroidetes, Proteobacteria, Verromicrobia, Actinobacteria, Fusobacteria and Cyanobacteria.[12] Each microbe participates in many physiological processes, such as improvement of gut mucosal immunity, uptake and production of essential nutrients, maturation and maintenance of the GI sensory and motoric functions and defense against pathogens by antimicrobial compounds production. These defenses are mostly promoted due to the intestinal barrier integrity, constituted of an epithelium arranged in villus and the submucosal tissue with immune functions. The pathogens developed many attributes that allow them to damage and break this barrier, which gives access to the bloodstream and, consequently, other tissues and organs, ending in the putative participation of intestinal pathogens in the systemic disease's pathogenesis.[13,14]

Given the scientific evidences of oral bacteria presence in extra-oral sites in disease conditions, many authors hypothesized the plausibility of an oral-gut axis in these cases.[10,15,16] By swallowing an oral pathogen, its presence in gut microenvironment causes homeostasis disturbance, a situation called dysbiosis.[17] Dysbiosis is a sufficient trigger for the intestinal barrier imbalance, raising bacteria or bacterial products to spread through the bloodstream.[18,19] The enteral route as a pathway of ectopic gut colonization by oral bacteria is supported by the amount of oral strains found in maladies and health patients stool samples, such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Klebsiella* spp., *Veillonella* spp., *Prevotella* spp., *Streptococcus* spp. and *Aggregatibacter* spp.[10,20] The virulence compounds excess in the blood causes endotoxaemia and contributes to the production of acute phase proteins at the liver.[21,22] These mediators are known to act in systemic conditions, such as heart diseases, diabetes and pregnancy complications.[15,18] Besides the metastatic inflammation, the gut pathogens have the potential to stimulate T helper 1 (Th1) lymphocytes subpopulation differentiation, which has a pro-inflammatory profile.[16] Likewise, the oral inflammation per si is responsible for a huge production of pro-inflammatory cytokines and its presence in plasma also affects health homeostasis. Proinflammatory mediators, such as IL1â, IL6, TNFá and PGE_2, produced locally in the inflamed gingival tissues may "spill" into the circulation and have systemic impact, such as induction of endothelial dysfunction.[23] Oral bacteria, disseminated from periodontal, endodontic or mucosal lesions, can survive in the bloodstream and may adhere at nonoral body sites. Since the gut microbiota and oral microbiota directly or indirectly influence the evocation of systemic diseases, may the use of probiotics protect intestinal barrier damage and prevent bacteria to spread through the bloodstream, avoiding systemic complications. Therefore, the gut microbiota modulation can cause oral health and vice-versa.[24]

Caries: Cariogenic Biofilm Specificity and Risk Factors

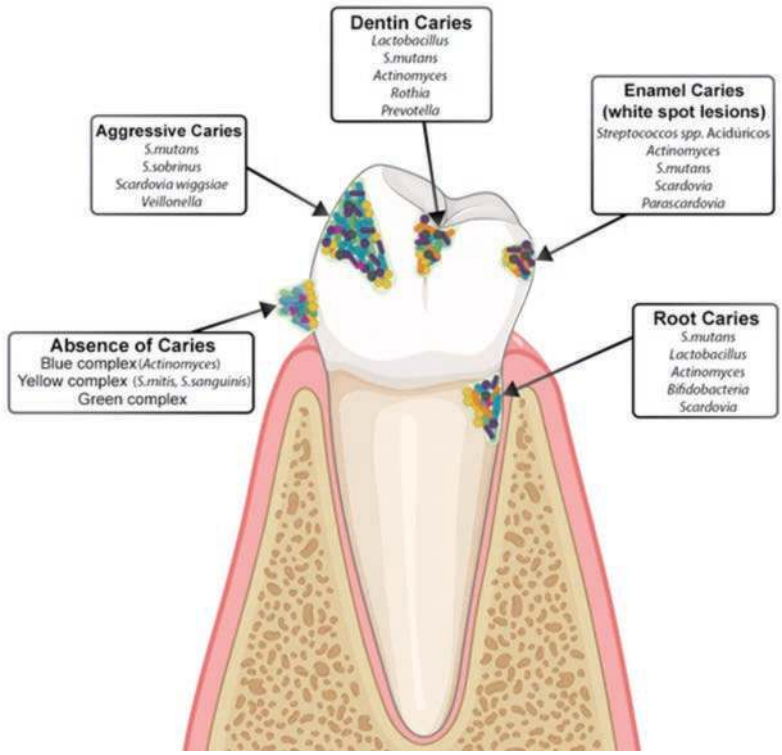

***Figure 1**: Biofilm Relationship in types of Dental Caries in a Symbiotic and Dysbiotic state. Incorporating concepts of Takahashi and Nyvad (2016); created with Biorender (2020). Source: Nascimento's personal* archive.

Caries is a multifactorial disease, modulated by a dysbiotic and sugar-dependent process that promotes teeth demineralization and destruction, and may also cause endodontic complications or to dental element loss (Figure 1).[2,25,26,27] This is a progressive and transmissible infection characterized by mineral teeth loss due to long exposure to acidic *pH* due to the oral bacterial metabolization dietary carbohydrates. This dysbiosis begins due to a deregulation of the homeostasis of the oral microbiota favoring aciduric and acidogenic microorganisms.[28,29]

Cariogenic Biofilm (CB) is composed by acidogenic and acid-tolerant species and classified in streptococcal and non-streptococcal species. The first group is formed mainly of *Streptococcus* spp., especially *S. mutans* and *S. sobrinus*, and the second presents itself with the participation of *Lactobacillus* spp., *Bifidobacterium* spp., *Scardovia* spp., *Actinomyces* spp., *Veillonella* spp., as well as fungi (for example the *Candida albicans*, which has a coaggregation with *S. mutans* in the presence of sucrose, in which there is a beneficial bidirectional action between its virulence factors and biochemical characteristics favoring both species). Gram-negative anaerobic species such as *Prevotella* spp., *Porphyromonas* spp. and *Selenomonas* spp. have been associated with deep caries lesions in dentin. These species interact in a dynamic microbial synergistic relationship within the biofilm.[30,31,32]

The diet factor is important to be considered because the high carbohydrates intake influences the biofilms formation. The fermentation of food carbohydrates, mainly sucrose, favors the glycosyltransferases production to catalyze the synthesis of extracellular polysaccharides and acid metabolites, selecting the predominance of acidic and acidogenic species. What results in a CB with pathogens capable of producing acids that demineralize teeth enamel.[33,34]

Although there are several biological risk factors that directly influence caries, the relationship of how the diet affects the oral microbiota and the composition of dental biofilm plays a critical role in this infection development.[35,36]

Periodontal disease: periodontopathogenic biofilm specificity and risk factors

Periodontal Disease (PD) is a multifactorial disease, modulated by a dysbiotic and an inflammatory process that directly affects the teeth supporting tissues and is the second cause of teeth loss in the world with prevalence in up to 70% of the population.[27]

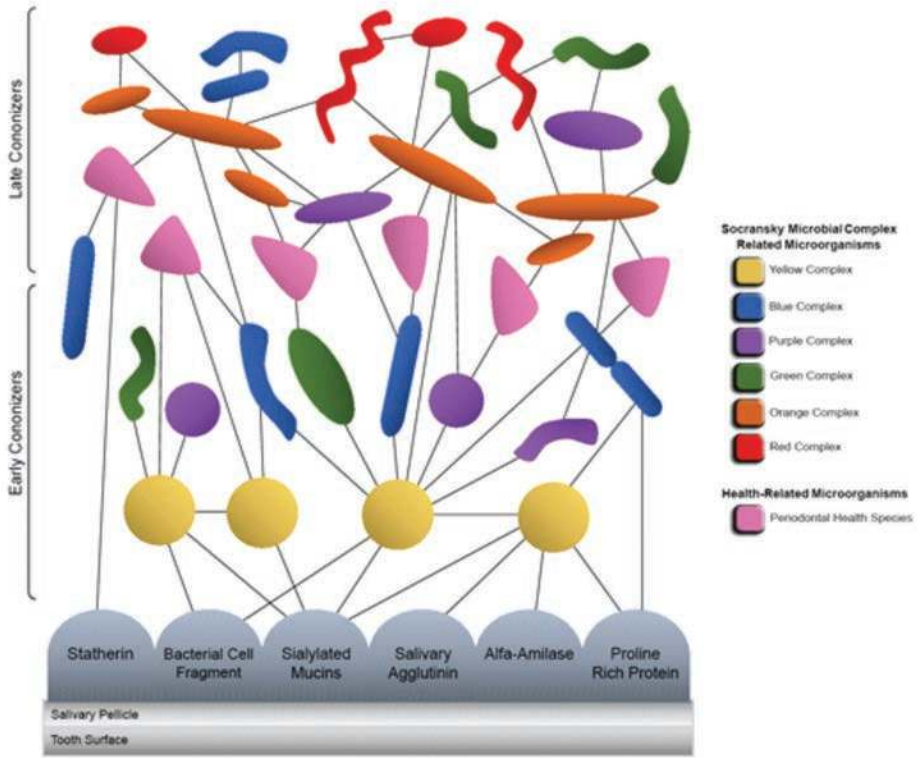

***Figure 2**: Symbiotic Supragingival Biofilm Scheme. Incorporating concepts of Socransky Microbial Complex (1988), Kolenbrander and collaborators (2010) and Colombo & Tanner (2019). Source: Nascimento's personal archive.*

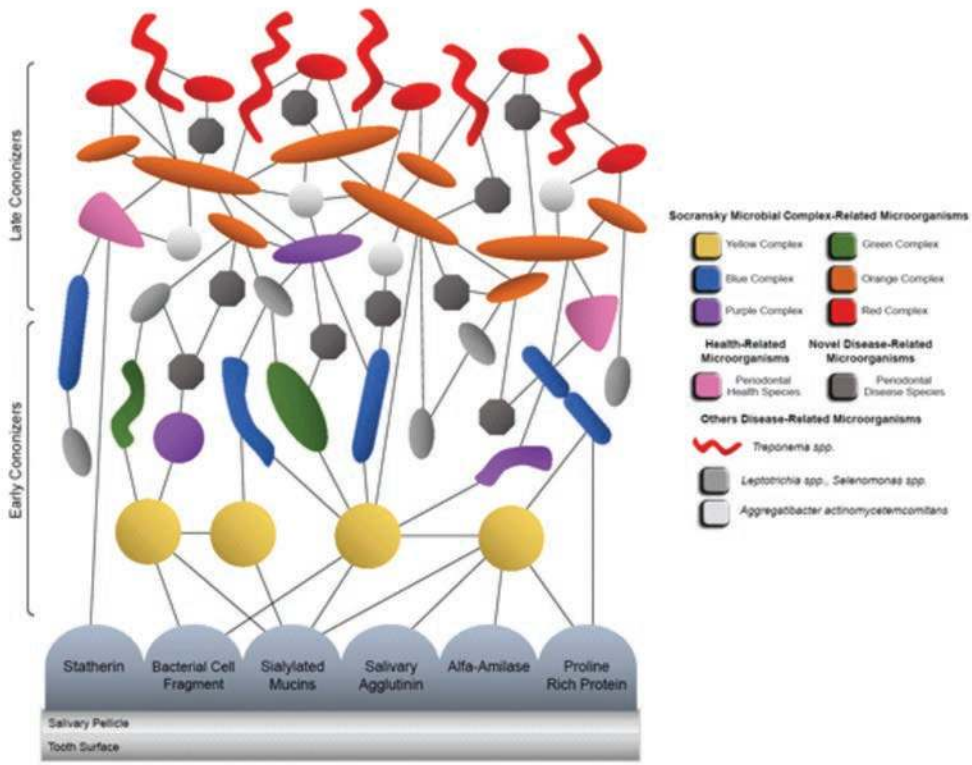

***Figure 3**: Dysbiotic Subgingival Biofilm Scheme.* Incorporating concepts of Socransky Microbial Complex (1988), Kolenbrander and collaborators (2010) and Colombo & Tanner (2019). Source: Nascimento's personal archive.

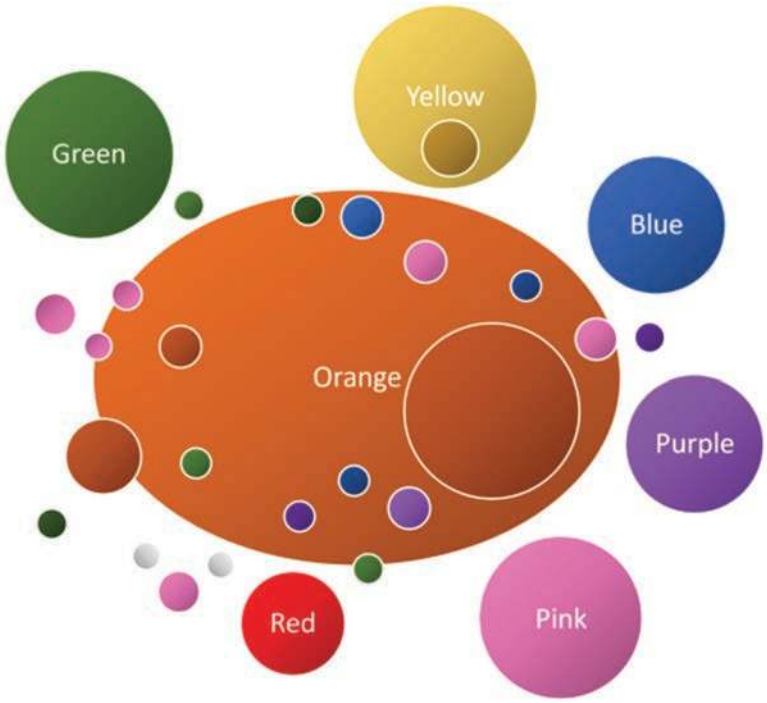

***Figure 4**: Socransky Microbial Complex. Microbial Complex established by Socransky and collaborators (1988) adapted with concepts by Colombo & Tanner (2019). Source: Nascimento's personal archive.*

Periodontal biofilm is a non-randomly organized microbial community adhered to the tooth surface under the gingival line involved in a glycoprotein matrix and composed by true periodontal pathogens and health-related microorganisms (Figure 2).[37] The progress of the disease's onset, the oral microbiome virulence begins to increase and the host resistance decrease, which is where opportunistic pathogens and disease-related microorganisms will give specificity to a Periodontopathogenic Biofilm (PPB) resulting in a dysbiosis process of oral microbiota, eventual teeth loss and can also affect the systemic health. The PPB itself acts as a virulence factor generating harmful bacteriocins and designating greater resistance to them (Figure 3).[38]

There is a high diversity in the PPB, which is composed predominantly of gram-negative, proteolytic and anaerobic bacteria.[39] In disease state, there is a red complex prevalence (*Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola*), as well as the orange complex, as described by Socransky (1998) (Figure 4), and other medical importance bacteria that act as opportunists in the middle of the dysbiotic process generated by PD. Periodontal biofilm has its own life activity, a biofilm lifestyle. There are specific interactions between microorganisms within the biofilm, based on shared characteristics and symbiosis relationships. Thus, the interaction between microorganisms in the periodontal biofilm functions as a symbiotic feedback mechanism among species.[40,41,42,43] For example, the symbiotic relationship between *T. denticola* and *P.gingivali*s. The first one ferments the amino acids from the subgingival biofilm and produces succinate (used to coagulate the surface by *P. gingivalis*), while the second produces some fatty acids that favor the proliferation of *T. denticola.*[44]

Furthermore, the absence of oral biofilm control causes changes in the oral microbiota favoring pathogenic complexity, since PD has a biofilm-dependent load and maturity correlation. Thus, the pathogenic microbiota and PD mediators of chronic inflammation contribute to the development or continuity of chronic inflammatory diseases in a bidirectional relationship.[45] Although, there are risk factors that aggravate PD, such as smoking, type 2 diabetes, bad habits of oral hygiene, high consumption of alcoholic beverages, obesity, psychosocial factors and high blood pressure.[46] In addition to these risk factors, malnutrition can stand out as an influential factor that can influence the oral microbiota.[3]

Nutritional health: influence and impact of macro and micronutrients in oral-systemic health perspective

Nutrition is considered one of the main pillars for human development, based on the food-body relationship. The nutritional status is directly associated with the adequate supply of macronutrients (carbohydrates, fats and proteins) (Table 1) and micronutrients (vitamins, minerals and others), especially for the proper functioning of cells and the systems'

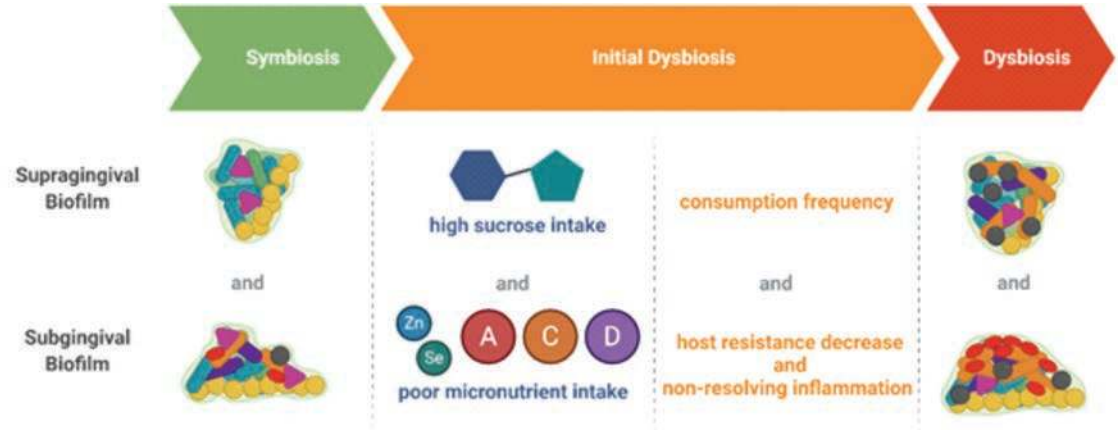

***Figure 5**: Nutritional Influence on Supragingival and Subgingival Biofilm.* The supragingival biofilm in Symbiosis is in homeostasis. In Initial Dysbiosis begins the dysbiotic state due to high sucrose intake and high frequency of consumption (time factor), thus not allowing pH buffering. In Dysbiosis, the characterization of the cariogenic biofilm already exists. The subgingival biofilm in Symbiosis is compatible with periodontal health. In Initial Dysbiosis due to the influence of poor micronutrient intake, the immune system and the host's responses are compromised generating a destructive inflammatory response induction. In dysbiosis there is already a characterization of periodontopathogenic biofilm; created with Biorender (2020). Source: Nascimento's personal archive.

homeostasis. According to the World Health Organization (WHO): "Nutrition is the science of food and its relationship to health" and "Malnutrition is the cellular imbalance between the supply of the nutrients and the energy and the body's demand for them to ensure growth, maintenance, and specific functions". There is a strong association between the role of nutrition and OH conditions with many interrelating factors. Furthermore, understanding the main aspects of nutrition is essential for an individual's health.[4,47,48]

The systemic nutritional factors have an important OH impact, especially during the period of tooth development, it affects cellular metabolism, protein synthesis, and other biochemical processes like calcification. For instance, proteins are an essential macronutrient, and they are important to the body throughout life, as it secures muscle and bone metabolism, ensures the maintenance and development of a normal nervous system, and helps to sustain muscle mass and physical performance in older ages, for instance. In addition, carbohydrates are considered organic compounds whose main function is to provide energy supplies for the body; fats are components of adipose tissue, cholesterol, hormones, nervous tissue, cellular components (phospholipids) and other structures. Imbalance on these macronutrients or micronutrients status may interfere in OH conditions and lead to oral diseases development.[49,50,51]

The relationship between nutrition and OH has been discussed in many studies. Diet is considered one of the risk factors for caries and enamel erosion, also nutritional imbalance impacts on teeth development and the host's resistance to many oral conditions, such as PD. Furthermore, these aspects play essential roles in the OH, in the integrity of the gum and mucous membrane, in the strength of the bones as well as in the oral infections' treatment. Therefore, NH may affect the development and maintenance of the oral and dental tissues. As we have seen, diet can intervene the tooth integrity; the type, shape and frequency of foods and drinks consumed affect, directly, the oral *pH* and microbial activity, which can promote dental caries (Figure 5).[5,59,67]

Nutrition and diet are associated with the oral cavity's integrity, also nutrition imbalance may lead to disease progression in the OH, reduce resistance to oral bacteria and prevents tissue healing and it may directly affect its development on early life (Table 2).[68,69]

The periodontal defenses are influenced by proper functioning of the host's humoral and cellular immune system, the phagocytic system and the integrity of the oral mucosa. The crevicular and junctional epithelium build an epithelial barrier function and it provides a major defensive barrier against invasion by antigens, pathogens or noxious products. It undergoes a rapid turnover and is therefore dependent of good nutritional status. In addition, systemic factors associated with the PD initiation or progressions include diabetes mellitus, osteoporosis and osteopenia, stress and inadequate coping, and the periodontal pathogens presence in the subgingival microbiota.[72,73,74]

Moreover, the pro resolving lipid mediators, resolvins and protectins with anti-inflammatory and immunoregulatory actions are biosynthesizes from metabolism of ù-3, through cessation of proinflammatory cytokines production and regulating the recruitment of inflammatory cells to the inflammation sites, thus enhancing clearance of inflammation within the lesion to promote tissue regeneration. However, a recent research showed a broad range of antibacterial activity for both Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), including the inhibition of putative periodontal pathogens, such as red and orange complex. As well as futures therapies with long chain ù-3 PUFAs may therefore combine periodontitis treatment with an anti-inflammatory and antimicrobial approach.[75,76]

***Table 1**: Macronutrients and Oral and Systemic Relationship.*

Macronutrient	Oral and Systemic Impact	References
Carbohydrates	Some studies have been suggesting that diets high in refined carbohydrates trigger a hyperinflammatory state evidenced in caries and PD. Also, sugars and other fermentable carbohydrates are metabolized to bacterial biofilm acids, resulting in low pH and it is favoring the growth of the acidogenic and aciduric species. Hence, the dynamic enamel mineral loss is initiated for acid produced CB metabolizing fermentable carbohydrates, so they may interfere in the demineralization-remineralization process. Besides that, carbohydrate consumption or biofilm accumulation can perturbate the oral microbiota and lead to the oral infection's development. In contrast, a diet rich in complex carbohydrates and soluble fibers may reduce the risk of periodontitis and disease progression, especially among older adults. Also, they are associated with greater insulin sensitivity and lower risk of diabetes and metabolic syndrome. In fact, this relationship is important, especially because some studies showed the relation between periodontitis and hyperglycemic state, also the association between dietary fiber intake and periodontal health.	**Salazar et al., (2018)[52]; Bernabé et al., (2016)[53]; Zhan (2018)[54]; Nielsen et al., (2016)[55]; Laiola et al., (2020)[56]**
Fats	There are two major families of Polyunsaturated Fatty Acids (PUFAs) and they are involved in the inflammatory process. In addition, omega-3 (ù-3) derived mediators might lead anti-inflammation effect, while most of omega-6 (ù-6) derived mediators aggravate inflammation, these effects may affect directly if in a balanced diet. Western diets are typically ù-6 rich (soy, cereals, sunflower oil, and animal products) and present low sources of the ù-3 fatty acids, consequentially, they promote low concentrations of ù-3 PUFAs through conversion to arachidonic acid in our body. Moreover, ù-3 fatty acids include á-Linolenic Acid (ALA), Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) that are in high concentrations especially in fish oil, linseed, and walnut oil. The EPA and DHA serve as important precursors for gene expression, inflammatory processes and lipid-derived modulators of cell signaling. Also, the synthesis of ù-3 polyunsaturated fatty acids in humans is limited and it is considering an essential dietary component.	**Calder, (2017)[57]; Azzi et al., (2018)[58]; Kruse et al., (2020)[59]; Iwasaki et al., (2011)[60];Dawson et al., (2014)[61]**
Proteins	Disorders in protein metabolism can affect the matrix formation of both enamel and dentin in the developing tooth as well as formation of the intercellular matrix of the fibrous periodontal ligament, alveolar bone, and cementum. Proteins have an important effect on satiety and reduce simple carbohydrates consumption such as sugar, e.g. Also, studies have showed association between dental caries and dietary habits, especially high consumption of these types of carbohydrate. Alterations in dietary protein intake may impact muscle and whole-body protein balance, negatively impacting muscle mass maintenance, and its function. Moreover, obesity and overweight conditions directly affect body-composition, especially contributing to the increase of adipose tissue and consequently reduction of muscle mass. Therefore, these conditions promote a disbalance on inflammatory state (pro-inflammatory cytokines) and an increase of oxidative stress by adipose tissue, and associate with PD, this inflammation may increase gingival inflammation and promote bacterial proliferation on the tooth's root surface. Some studies reported the beneficial effects of dietary protein on glycemic control. This relation may assume an important role in PD, and also influence the systemic inflammation.	**Carbone et al., (2019)[62]; Drummen et al., (2018)[63]; Hopkins et al. (2016)[64]; Martines Herrera et al., (2017)[65]; Khan et al., (2018)[66]**

***Table 2**: Micronutrients and Oral and Systemic Relationship.*

Macronutrient	Oral and Systemic Impact	References
Vitamins and Minerals	Vitamins are catalysts for all metabolic reactions, using macronutrients for energy, growth and cell maintenance. They also function as electron donors, antioxidants, and transcription effectors. Vitamins are categorized into 2 major groups: fat-soluble (A, D, E and K) and water-soluble (B-complex and vitamin C). Minerals serve as structural or catalytic components of enzymes and regulate cellular energy transduction, gas transport, antioxidant defense, membrane receptor functions, second-messenger systems, and integration of physiologic systems. Minerals can be classified as either major minerals (>100 mg/day) or trace elements (<100 mg/day). The major minerals are sodium, potassium, calcium, magnesium, phosphorus and sulfur. The trace minerals are: iron, zinc, iodine, selenium, fluoride, copper, cobalt, chromium, manganese and molybdenum. Thus, a fast-immune response, especially in the case of inflammatory process, present in some oral infections like gingivitis and periodontitis, may be limited with insufficiency of nutrients, i.e., malnutrition. This condition may influence the immune system's function, especially on innate and adaptive defenses of the host, including cell mediated immunity, phagocytic function, secretory antibodies, complement system, and cytokines action. it can intensify the severity oral infections and lead to their evolution of many diseases. As well as impacts on OH may affect daily dietary intake, which consequently degrades the nutritional balance and general health. Furthermore, it has a negative impact especially on the quality of life since the diet influences the individual's food choices.	**Shay et al., (2019)[68]; Cagetti et al., (2020)[69]; Uwitonze et al., (2016)[70]; Badrasawi et al., (2020)[71]; Hujoel et al., (2017)[72]**

Functional role of probiotics and prebiotics in oral and systemic health

"Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host".[77] There are numbers of probiotic characteristics that can promote OH. We hypothesize that oral probiotic may compete for nutrients and/or buffer the oral *pH* towards a more neutral *pH*, reducing the numbers of opportunistic pathogens, may limit the dental biofilm progression by bacterial co-aggregation and by the antibacterial substances production, such as bacteriocins and nitric oxide. It is also possible the adherence to the oral surfaces, outcompeting pathogen adhesion and proliferation.[1]

When ingested, probiotics reach the GI tract and exert many effects, such as modifying the gut microbiota, improving the intestinal barrier function and the immunity, resulting in systemic benefits. Probiotics have been intensively studied due to their amount of benefits on many human and animal diseases, participating in the treatment scheme for acute infectious diarrhea, Irritable Bowel Syndrome, Ulcerative colitis, Crohn's disease, atopic dermatitis and psoriasis.[78,79]

Commercial probiotics are, generally, presented as fermented foods, such as milks, yogurts and cheese. They can be classified in the functional foods group, particularly in the division of the Dairy Products. Functional foods are those that when consumed regularly exert a specific health-beneficial effect beyond their nutritional properties, and this effect must be scientifically proven. Functional foods are similar to conventional foods, which are consumed as part of a usual diet but are known to improve health status beyond primary nutritional function.[80]. The Functional foods provide ways to reduce the increasing burden on the health care system by continuous preventive mechanisms, including about OH, coupled with public interest and consumer demand.

The major microbe groups present in probiotics include the Lactic Acid Bacteria (LAB), *Bifidobacterium*, the yeast *Sacharomyces cerevisae*, *Bacillus* spp. and a strain of *Escherichia coli.*[81] The LAB group's composition accomplishes *Lactococcus*, *Enterococcus*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Leuconostoc* and *Lactobacillus* species.[82] Typically, LAB are found as dominant organisms in many spontaneous fermentations of food and feed.[83]

The capacity to adhere and colonize the oral surfaces

is a crucial condition for a microorganism to be elected as a great probiotic for OH. The main microbial groups used as oral probiotics include the genus *Lactobacillus*, *Bifidobacterium*, *Lactococcus* and *Streptococcus*. An important issue found among the studies is that the probiotic that has effect is strain-specific and disease-specific efficacy, which means that a bacterial specie known as a pathogen member can be a good strain having a probiotic effect probiotic effect on a given disease.[84] *Escherichia coli* is an example, commonly regarding a gut microbiome member and pathogen, but studies showed the probiotic effect of the Nissle strain 1917, which colonizes the mammalian gut.[85]

The use of probiotics in dentistry for oral therapy has become increasingly frequent and aim to reestablish the biofilm equilibrium, which acts as a cascade trigger events that constitute the oral diseases spectrum. The following mechanisms of probiotics action in the oral cavity are: direct interaction with dental biofilm, oral microorganisms binding to product proteins and intervention/competition in bacterial adherence and ecology plaque formation.[86,87]

Corroborating the inhibitory probiotics effect against oral pathogens, Shin, Baek and Lee (2018) demonstrated that *Lactococcus lactis* has antimicrobial activity against periodontopathogens, such as *F. nucleatum*, *P. gingivalis, T. forsythia* and *T. denticola* using the culture supernatant as well as performing co-cultivation. In addition, neutralizing activity on the production of volatile sulfur compounds was observed, as well as a reduction in the pro-inflammatory cytokines production from cells challenged with LPS of these pathogens.[88] Chen (2020) also showed the antibacterial activity of viable and heat-killed probiotic strains (*Lactobacillus salivarius* subsp. salicinius AP-32, L. *rhamnosus* CT-53, L. *paracasei* ET-66 and *Bifidobacterium animalis* subsp. lactis CP-9) against oral pathogens, such as *Streptococcus mutans, Porphyromonas gingivalis, Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans.*[89]

Studies about prebiotics are extremely recent yet, and also, it's exact role in the microbiome balance improvement in the human body is still unknown. However, some researches have been demonstrated to be already an aid to complement prebiotics in the oral disease's treatment. Currently, the term prebiotic is defined as "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gut microbiota, that confer benefits upon the host well-being and health". Moreover, the resistant Oligosaccharides-Fructo-Oligosaccharides (FOS) and Galacto-Oligosaccharides (GOS) are considered nondigestible carbohydrates, two existing prebiotic dietary fiber types. Prebiotics could stimulate the beneficial bacteria growth and suppress the pathogens growth in the gut microbiota. Also, they could improve the mucosal barrier function, enhance the production of Short-Chain Fatty Acid (SCFAs) and influence the host's immunity. For this reason, probiotics and prebiotics may be considered an important strategy, especially because they can reestablish the ecological balance regaining the intestinal and oral microbiota biodiversity in the early stages. This maintenance also contributes to reduce levels of inflammatory mediators and the host's immune responses.[8,90,91]

The nutrition impact on the oral microbiota modulation

In addition to other risk factors for Caries and PD, NH has an influence in modulating the oral microbiota's composition and function, as well as OH, acting as a perspective not only of treatment, but as a preventive role maintaining microbiome homeostasis. In this sense, the use of probiotics and prebiotics nutrition therapy has been shown to be very effective in the treatment of these oral infections as opposed to the antimicrobials use. To support this concept, this review determined the impact of nutrients on oral and systemic health and it was observed that there is a pre-existing bidirectional relationship between the oral-systemic axis. And, although all nutrients have their importance and specific effects for OH homeostasis, micronutrients proved to be of greater relevance.

Colombo and Tanner[27] showed that dental biofilm assumes a very influential role in the oral infections' etiopathogenesis. Oral diseases, such as Caries and PD, should not be seen as caused by one or some true pathogens as described in classical infections, but as a polymicrobial holistic community that has the potential to trigger dysbiosis of microbial community, due to changes in complexes mechanisms between microbiota-environment-host.

Some studies have raised the hypothesis that dysbiotic oral microbiota may disturb the gut microbiota at the long-term period. The high ingestion of oral pathogens may induce a dysbiotic process in the gut microbiota and a systemic inflammation state, endotoxemia, insulin resistance, high dysfunction of glucose levels and a hypofunction of the intestinal barrier. In contrast, the disturbed gut microbiota is able to modulate the severity and frequency of oral infections.[51,92,93]

About the association between OH and NH, Hugar[94] demonstrated an association between deficiencies or inadequate micronutrient intake with the increase susceptibility to caries and DP. Bhargava[95] declares that vitamin D plays a crucial role in bone maintenance and immunity, and the imbalance of its status in the body can induce dentin and enamel defects during tooth development

and it could negatively affect the periodontium. Adegboye[5] declares that malnutrition can elicit adverse alterations in volume, physiochemical and antibacterial properties, which may have consequences on the *pH* and oral microbiome. In summary, this synergy between nutritional status, OH and dietary practices combined with removal of the inflammatory periodontal stimuli is important to diminish the severity of PD. Also, Shay[68] showed that the nutritional status has a direct influence on the immune system. In turn, it affects the innate, adaptive and cellular immune responses, especially the protection against host invasion by microorganisms and inflammatory response. Undernutrition and nutrient deficiency suppress immune functions, compromising the synthesis and the release of cytokines and their action. Consequently, when associated with increased needs for calories, protein and micronutrients promote repletion, that replicates immune cells, balance of antioxidant and oxidants agents, wound healing, and an improved immune response (Figure 5).

Another important role of nutrients in the host are the benefits of ù-3 fatty acids in inflammatory response. However, researches about the cellular and molecular mechanisms underlying their host modulatory action with use of long chain ù-3 fatty acids are still largely unknown in various systemic diseases.[96] The majority of PUFAs from dietary are usually used to construct phospholipids present in cell membranes, and they act as precursors for lipid mediators involved in cell signaling and contribute to the cell's membrane integrity and fluidity. Omega fatty acids are the PUFAs, and they had three major types of ù-3 derived from food and used by our body, especially, EPA acid and DHA.

Zohoori & Duckworth[97] points another relevant aspect, vitamins are essential organic compounds and biologically active constituents of a diet. Also, they are catalysts for the body's metabolic reactions; they also function as electron donors, antioxidants, and transcription effectors. The absence or scarcity of certain vitamins has been implicated as being etiological factor in the PD's pathogenesis. Tada & Miura[98] have shown that vitamin C deficiency may result in lack of collagen formation by affecting hydroxylation of proline and increased permeability of endotoxin from the oral mucosa. Also, this vitamin has an antioxidant potential in the body's defense system, it is directly neutralizing free radicals, scavenging the hydroxyl radicals which mediate tissue damage, and suppressing macrophage secretion of superoxide anions. As a result of this, vitamin C can be considered an important nutrient present on the dietŻ for periodontal health, and it has capacity to control excessive Reactive Oxygen Species (ROS) produced in oral infections.

Following this line, the probiotic and prebiotic supplementation can influence and play an important role in the oral infection's treatment and prevention. Corroborating the inhibitory effect of probiotics against oral pathogens, Dassi[99] showed that the saliva microbiome enhanced its diversity after probiotic intake, and the principal effect of probiotic bacteria to reduce the caries risk is inhibition of CB formation by killing the pathogens (bacteriocins, growth inhibition) or avoiding their co-aggegation. Given the dysbiotic biofilm nature of the dental caries, the inhibition of a single pathogen makes little sense, so a great probiotic essentially needs to act on different members of an oral community.

Hedayati-Hajikand[100] study evaluated the effect of probiotic chewing tablets on early childhood caries development in preschool children living in a low socioeconomic multicultural area. They concluded that caries development could be reduced through administration of these probiotic chewing tablets as adjunct to daily use of fluoride toothpaste. Short-term consumption of *Lactobacillus rhamnosus* GG, *Limosilactobacillus reuteri*, and *Bifidobacterium lactis* BB-12 have reduced counts of *S. mutans*, the major caries pathogen.[101] More trials are needed to gain better knowledge of probiotic supplements and to confirm that their use is beneficial and cost-effective in caries care.

Esteban-Fernández[102] published their results about the beneficial effects of *Streptococcus dentisani* as potential oral probiotic for PD. This specie was found at high levels in the gingival crevice, inhibiting the periodontal pathogens by competition, adherence and displacement mechanisms. Besides that, the oral probiotic increased the secretion of the anti-inflammatory cytokine IL-10 after incubations with oral pathogens in a simple *in vitro* model. Another specie showed probiotic effect: Garcia[103] presented *Saccharomyces cerevisae* as a monotherapy and as an adjuvant to the mechanical treatment of experimental periodontitis in rats and it showed positive effects. Theodoro et al[104] evaluated the effect of *Lactobacillus reuteri* in chewable tablets as an adjunct to non-surgical periodontal treatment of chronic periodontitis in smoking patients. The adjuvant use of *L. reuteri* in the treatment of chronic periodontitis was effective in controlling gingival inflammation because it reduced bleeding on probing, which means it reduced gingival inflammation and was effective in reducing deep pocket in a clinically relevant manner.

Shin et al[88] demonstrated that *Lactococcus lactis* has antimicrobial activity against periodontopathogens, such as *F. nucleatum, P. gingivalis, T. forsythia and T. denticola* using the culture supernatant as well as performing co-cultivation. In addition, neutralizing activity on the production of volatile sulfur compounds was observed, as well as a reduction in the pro-inflammatory cytokines production from cells challenged

with LPS of these pathogens. Chen[89] also showed the antibacterial activity of viable and heat-killed probiotic strains (*Lactobacillus salivarius* subsp. salicinius AP-32, *L. rhamnosus* CT-53, *L. paracasei* ET-66 and *Bifidobacterium animalis* subsp. lactis CP-9) against oral pathogens, such as *Streptococcus mutans, Porphyromonas gingivalis, Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans.*

Nevertheless, Almoznino[105] evidences nutritional imbalance effect on cellular and molecular levels, oral biofilms, tissue metabolism and immune response, suggesting that nutrition has the potential to affect biological gradient and thus affect periodontal infections. Accordingly, PD develops faster in undernourished populations. Food intake is not a treatment for oral and dental infection, but depleted nutrition can negatively impact tissue integrity, mineralization, progressive damage to mucosa, as well as a diminished resistance to colonization and invasion by pathogens and other aspects that had been previously described.

CONCLUSION

This study concluded that malnutrition is an important risk factor to be considered in the oral infection's treatment and that it should receive more attention by the Dentist. The macronutrients and micronutrients' frequency of ingestion is able to modulate the oral microbiota and impact OH. The preventive character is more resolutive and effective than during the treatment itself. NH is much more than just "dieting" and plays a key role in OH. In addition, supplementation with probiotics and prebiotics for the nutrition treatment of Caries and DP is shown with very satisfactory research that increasingly directs this treatment. However, more studies need to be done to better understand the nutrition and oral microbiota subject. Furthermore, it is up to the Dentist to allow itself a holistic look, to study to the point of knowing what to ask the patient about NH, to think how far it can go and to know when it is time to refer to a Nutritionist or even make a joint multidisciplinary treatment.

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