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The oral and gut microbiota: beyond a short communication

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Abstract

Introduction. The current treatment and prevention of oral disorders, dental caries, periodontal and gum diseases, follow a very non-specific control of plaque as the main causative factor. The main therapeutically approach is carried out on the sole perspective to keep the levels of oral bacteria in an acceptable range compatible with one-way vision of oral-mouth health, as something completely separated from a systemic microbial homeostasis (dysbiosis) concomitant present in the gut. A sealed compartmental view which sees separate and incommunicable responses to a specific condition without considering the presence of interacting confounding factors can negatively influence the diagnosis a diseases and of course its progression. A general non-specific antimicrobial with more general antiplaque therapy based mainly on oral care products together with surgery interventions represent at the moment the only mechanical responses in treating oral diseases.

Material and method. The present paper is a narrative review concening interractions between oral and gut microbiota, with a focus on the interdisciplinary approach in antimicrobial treatment. Pubmed, Cochrane Library database were used for searching engines. Key words used were as follows: **"**inflammatory bowel syndrome (IBS)", "ulcerative colitis", "oral dysbiosis", "gut dysbiosis", "probiotics", "periodontitis".

Results and discussions. Literature research showed that there are few issues to be discussed the ever increasing resistance to antibiotics, the high consumption of industrial food and sugars and their negatively effect on gut and oral microbiota. There is a need to highlight and develop a novel philosophical approach in the treatments for oral diseases that will necessarily involve non-conventional antimicrobial solutions. Such approaches should preferably reduce the consumption of both intestinal and oral microbiota, that are intimately connected and host approximately well over 1000 different species of bacteria at 108–109 bacteria per mL of mucous and saliva. Preventive approaches based upon the restoration of the microbial ecological balance, rather than elimination of the disease associated species, have been proposed.

Conclusions. Having both oral-gut microbiota screened is an essential moment that influence the healthy immune modulatory and regenerative capacity of the body and, the new proposed formula integrates a wider screen on the patients where oral condition is strictly evaluated together with gut screen; therefore any proposed treatment will be inevitably sustained by the use of prebiotics and probiotics to promote health-associated bacterial growth.

Keywords: *inflammatory bowel syndrome (IBS), ulcerative colitis, oral dysbiosis, gut dysbiosis, probiotics, periodontitis,*

INTRODUCTION

A new direction in oral health treatment the immune-metabolic approaches

Despite of all negative aspects regarding isolation and socio-physical restrictions, pandemic difficult period was a good opportunity for studying disease physiopathology, immunologic aspects, human organism's interractions, focusing on finding prevention strategies (1-5). The fact that there is a strict connection between gut microbiota, oral microbiota and metabolic functions the healthy state of human metabolism has become a prerogative in medical practice. Principles such as 'mind and body medicine' are more and more adopted, considering that there is strong literatur evidence that a large number of diseases are psychosomatic (6).

In first instance, the body metabolism depends on a symbiotic relation of the whole types of bacteria, archaea, viruses, fungi, and host eukaryotic cells that colonize human gastrointestinal tract (GI) and that is known under the name of gut microbiota (7, 8). Moreover, upper part of GI tract communicates to respiratory system, contributing to bacterial variety and pathogenesis (9). The presence of these variegate forms of microorganism is vital for the life and evolution of human species, the main activity is to obtain from food essential nutrients compound for the production of great variety of bio-molecules, amino acids, hormones, vitamins and short-chain fatty acids (SCFAs). In addition supervise and control as perfect metabolic engines the whole system homeostasis from gut up to the brain through the regulation of connected other activities within cells, tissues and organs such as glycolysis, acid/Krebs cycle regulation and oxidative phosphorylation (10). Recent studies have been elucidating how gut microbiota eventually affect the oral microbiota. The mechanism start with the quality of ingested food that in turns affect microbiota that exert a direct or indirect stimulatory effect on immune cells, in particular, T cells, B cells, Dendritic (DCs) and macrophages (11-16).

Oral and gut dysbiosis are indicators of poor systemic health conditions such as the metabolic syndrome and other systemic chronic degenerativge diseases (17). The gut and oral cave have a strict and very unique relation with the metabolic syndrome that eventually conduct led to the insurgence of chronic degenerative metabolic condition such as type-2 diabetes, hypercholesterolemia, kidney decay, liver steatosis, cardiovascular break-down and neurodegenerative diseases (18, 19). Both gut and oral pathogens have the ability of migrate and locate well away from their original location due to chronic inflamed "leaky mucosa" they can pass through and via local oral and mesenteric blood circulation can enter into the systemic circulation (19, 20) (Fig. 1).

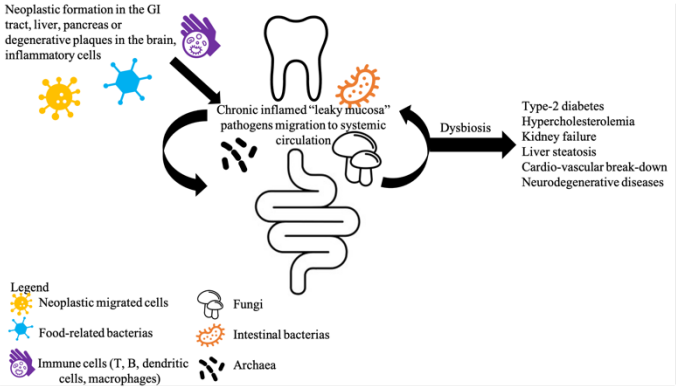

Fig. 1. Negative influence of oral cavity-gut dysbiosis on metabolic and inflammatory diseases onset and progression.

Macrophages are seen to migrate in chronic condition, the experimental outcomes showed their presence from oral location towards lungs (contributing to the respiratory impairment inflammatory profile), heart or even to brain scattering detrimental inflammatory responses that led to chronic tissue inflammation, infection and death (21, 22). Macrophage mobility is the result of their specific trait and high heterogeneity both in normal and in pathological conditions, and they can also lead to impaired metabolic profile (23). The macrophages are able to execute two main immune functions under local and systemic condition, they polarize into M1 the proinflammatory phenotype triggered by signal from LPS and Th1 proinflammatory cytokines and interleukins such as TNF-α, IFN-γ and IL-1β, IL-2, IL-4, IL-6 and IL-17 whereas immune-modulatory M2 phenotype triggered by Th2 cytokines IL-4, IL-5 and IL-13 as well as anti-inflammatory cytokines and interleukins like IL-10 and TGFβ, glucocorticoid and steroid hormones such as DHEA and estrogen (24-26).

The negative chronic activity scattered by an over expression of M1 phenotype is basically explained by the fact that dysbiosis is characterized by the presence of pathogens that use glucose as main source of energy subverting the activity of intracellular chemical mediators including the ATP together with an uncontrolled growth of reactive oxygen species (ROS) (24-26). However, this scenario suggests that once oral pathogens have crossed the mucosa barrier the body is already facing a systemic outbreak. The evidences are confirmed by the high presence of inflammatory and infection patterns caused by either pathogenic attack or high presence of inflammatory mediators which eventually results in a disease (27). Recently, last epidemiological studies showed that upper respiratory airways are sensitized by the presence of certain viruses, making tissue susceptible to infection (28, 29). Furthermore, many are the lines of evidence that have strongly confirmed the cross-talk

existent between oral and gut dysbiosis and the consequent insurgence of neoplastic formation in the GI tract, liver, pancreas or degenerative plaques in the brain (30). The histo-pathology outcomes provided the unconfutable proof oral/gut pathogens in the affected organ and surrounding tissues (27-30) (Fig. 2).

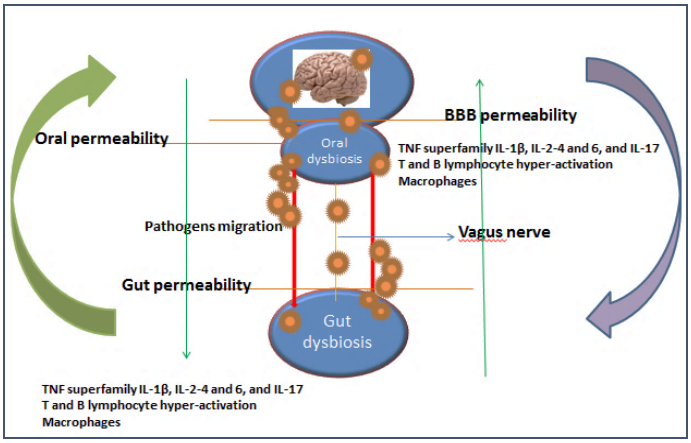

Fig. 2. The strict connection between CNS and Gut-Oral microbiota. This connection has physical connection through the afferent and efferent pathways of *Vagus* nerve CNS and Gut. Under microbiota dysbiosis CNS, Gut and Oral barrier become "leaky" or highly permeable allowing both pathogens and immune agents cross through scattering inflammations, infections and thus degenerations. Event that explains degenerative patterns and including IBS, ulcerative colitis, depression, Parkinson's disease, Alzheimer's disease and Multiple sclerosis.

As for the interractions with other humans' body organs and biofluids, dysbiosis is aggravated by the presence of ilicit substances (such as nicotine, canabinoids) and dysregulation of parasymphatetic and sympathetic nervous systems (31-34).

Material and Method

The present paper is a narrative review concening interractions between oral and gut microbiota, with a focus on the interdisciplinary approach in antimicrobial treatment. Pubmed, Cochrane Library database were used for searching engines. Key words used were as follows: "inflammatory bowel syndrome (IBS)", "ulcerative colitis", "oral dysbiosis", "gut dysbiosis", "probiotics", "periodontitis". Literature research resulted in 62 number of papers concerning the main subject.

Results

Regarding clinical manifestation from oral dysbiosis pathogens, here are always shared patterns found in these types of scenario, clinical and non-clinical symptoms usually start in patients mostly in their 40' and 50's with metabolic unspecific complaints, fatigue, food intolerance, fatigue, skin problems, oral mouth condition, aching joint and cognitive impairments. Dysbiosis also manifest in all cervicofacial structures, leading to acute/chronical soft tissue inflammatory diseases (temporo-mandibular joint disfunction, oral mucosa frailty, decreased turnover potential), impaired bone regeneration (which also affects subsequent treatment) and more important dental tissue microbial contamination (35-39). Also, modulated immune response could influence the microbial differentiation capacity and bactericidal effect (40, 41).

It must be highlight that the ageing process *per se* is contradistinguished by a progressive regression of beneficial commensal microbes that let over-growth the pathogenic commensal level thereby generating dysbiosis. A second common trait of these conditions is the presence of a chronic inflammatory state which negatively affects the regenerative mechanism impairing the apoptosis mechanism of normal somatic senescent cells, thereby enabling tumor and degenerative patterns development (27-30). Although no conclusive evidence have explicitly demonstrated the hypothesis between metabolic syndrome patients and brain degenerative patterns is driven by oral dysbiosis as cause of blood-brain barrier (BBB) dysfunction, the direct involvement of activated macrophages that crossed the BBB initiating local inflammatory responses has been under investigation and has given interesting clinical results. The idea is that collapsed BBB may follow a similar pattern found in impaired gut and oral mucosa barriers. The chronic inflammatory systemic condition of metabolic syndrome patients facilitates metabolic endotoxemia by increasing the permeability and therefore the uncontrolled passage of bacteria, immune cells such as macrophages and gut-oral derived endotoxins such LPS that in turns stimulate the activity of local microglia (42-49).

Discussion

Do probiotics will serve as therapeutic useful tools or they may just remain a myth? Despite existing controversial position on the topic, many lines of evidence and clinical studies have confirmed the validity of probiotics in the management of many condition either in gut dysbiosis such as IBS or oral dysbiosis such as periodontitis, there is a large increasing scientific support in using probiotic as therapeutic. Interventional studies have shown that the association of probiotics improves metabolisms' biochemical parameters, increase the level of benefic bacterias (lactobacilli and bifidobacterias), the level of immuneglobulines implicated in membrane defence (such as IgA) and Il-10 (with an anti-inflammatory effect) (48-50).

On the other side, oral cavity health is an important key factor not only for dental tissue development and function, prosthetic durability and mechanical properties, but also in bacterial spreading and multiplication (51-54). All the intervention performed on oral cavity's tissues, having thr purpose of improving oral status –

from dental hygiene training, mechanical plaque removal, use of additional antibacterial substances, up to etiological dental and periodontal initial therapy have as a first result the reduction of microbial load, but also the disruption of multiplication and needed nutrients and of course the degree of tissue oxygenation, an important factor in bacterial endurance (55-57). One of the most effective technology is laser therapy, which through its intensity, improves cellular adhesion (fibronectin, mesenchymal stem cells, collagen fibers), neovascularisation, infected wound healing and microbial count (58, 59). Red and near-infrared (NIR) lights improve tissue healing by downregulation of proinflammatory cytokines and increased angiogenesis (60). All the up-described mechanism reflect on gastrointestinal tract, through direct flow due to pharynx and aesophagus, and by means of vascular and lymphatic system. Previous studies have already proved there is a clear interconnection between oral and general pathology. More advance molecular diagnostic methodology has allowed investigating the systemic interferences and connections of the oral dysbiosis in human disease (61, 62). One of the presents' impediment is the lack of interdisciplinarity examination in GI chronical diseases, and the exiguous in consensus regarding treatment protocols targeting the same class of bacterias but with different location. Another hindrance is that usually medical practitioners interact with the patients in the acute phases of oral cavity and gut pathologies, and the focus in on eradicating the acute symptoms and control the disease. Moreover, the fact that microbes and toxins outreach several barriers and produce distance-related lesion is not taken into consideration. Majority of the treatment don't benefit of an initian microbiological examination, neither an inflammatory profile. This type of approach could enhance a treatment strategy based on early diagnosis and multiorgan-target, which will ultimately result in a controlled and improved oral and general health status.

Conclusion

The interaction of metabolic disturbances in oral microorganisms will surely help to understand the aggressive mechanism that from oral dysbiotic environment invade other organs or system. Studies in oral complex microbiota certainly will open up the possibility of better diagnosing and therefore treating chronic inflammatory degenerative diseases interconnected with oral pathogens.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions.

Berate Pula and Candrea Sebastian contributed equally as first co-author of this paper. Sirbu Adina and Cardarelli Fillippo contributed equally as last co-author of this paper.

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