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Perspective article

Emerging opportunity to implement host modulation therapy in non-surgical periodontal therapy-The role of probiotics and future perspectives

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Periodontal disease is very prevalent and poses significant chronic health burden on our patients. It is caused by polymicrobial dysbiosis leading to host-mediated inflammation and destruction on tooth-supporting tissue.[1] Since the primary pathogenesis of periodontitis is both the bacterial plaque and the host response, developing therapy modulating this host-microbeinteraction should a continuous pursue. Current established non-surgical treatment primarily focuses on mechanical debridement and bacterial reduction, including scaling and root planing with oral hygiene instructions. However, little has been implemented in the clinic regarding host modulation therapy. For patients with severe or stage III-IV periodontitis, deeper periodontal pockets usually require further surgical treatment,[2] but not every patient is a good candidate for surgical intervention, especially when patients are medically-compromised or smokers. Those patients oftentimes reveal unsatisfactory results after surgery. In this case, host modulation can therefore, enhance the outcome of the non-surgical periodontal therapy to avoid the need for surgical treatment. It is also essential to consider it during either active or compromised periodontal maintenance program, which may lower the risk for disease progression. With the new classification on periodontal diseases, modulating host response has already been a new focus. For example, by modulating host response by smoking cessation or improving blood sugar control, the patients could gradually be stabilized from Grade C to Grade B or even Grade A patients. This new two-dimensional classification system shed light on risk stratification and propose host response as the main driver for individualized disease and health trajectory. Developing new approaches for host modulation definitely is a new perspective and constitute contemporary comprehensive periodontal therapy.

Currently, available host modulation agents[3] includes: disease-modifying antirheumatic drugs (DMARDS), bisphosphonates (BPs), complement inhibitors, n-3 polyunsaturated fatty acids (PUFAs), specialized proresolving mediators (SPMs), statins, and probiotics. Many of which targets the bone resorptive mechanism and some counteracting the inflammatory response. Only probiotics targets both the host and bacterial component. Probiotics is live microorganisms that confer a health benefit on the host when administered with adequate amount, which was defined by the World Health Organization (WHO). Different classes of probiotics were identified and research has shown successful treatment in several field in medicine, including gastrointestinal tract and oropharyngeal infections.[4] The

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idea to develop probiotics to apply in oral health care started early[5] but not until recently more and more clinical trial has been conducted to explore its potential in serving as an adjunct for treating periodontal disease.

A recent systematic review[6] on the adjunctive use of probiotics included 24 randomized controlled clinical trials (RCTs), assessing the efficacy of using probiotics as adjunctive therapy to non-surgical periodontal treatment. The compiled data demonstrated positive results in terms of periodontal pocket depth (PPD) reduction, clinical attachment level (CAL) gain, and bleeding on probing (BOP) reduction up to 3 months, indicating immediate efficacy for general application. Additionally, a subset of studies showed significant clinical improvements in deeper pockets and confers stronger and longer-term clinical benefits as well as reducing the need for flap surgeries. Back in 2020, a systematic review with a similar clinical question was published but only consist of 10 RCTs. At that time, due to the limited available studies, the results were still inconclusive. Additionally, one must note that PPD is not the only parameter to monitor disease status or risk of progression. Most studies also showed pronounced improvement in BOP reduction. One of the classic landmark studies among navy sailors, 72 subjects were recruited into two groups with placebo control and observed at 14 and 42 days. In the test group with the consumption of probiotics, most of the clinical parameters significantly revealed better conditions than in the control group, especially bleeding on probing.[7]

There are several mechanistic studies on how probiotics may help modulating the host response or the symbiosis of the biofilm. Certain *Lactobacillus* probiotics can compete with periodontal pathogen *P. gingivalis* to adhere with the epithelial cells and thus preventing its adherence and invasions of the host cells.[8] Despite every strain may behave differently, probiotics in general can inhibit destructive inflammation, increase anti-inflammatory mediators, and foster a favorable environment for periodontal tissue homeostasis.[9] It modulates the host by regulating immune-related gene expression, inhibiting the NF-kB pathway to decrease pro-inflammatory cytokine production, and promoting Treg increase by inhibiting histone deacetylases.[3] Therefore, probiotics not only just competes with the pathogens in the microbiome but also modulates host immune reactions.

Some pilot studies also investigated whether modulation of the microbiome can be feasible or sustainable. One must note that there are several reservoir or sampling source for oral microbiome, including saliva, tongue, supra, or subgingival plaque. If investigating anaerobic pathogens, subgingival plaque sample should be considered. For example, in Laleman et al.,[10] different samples were collected and only subgingival samples showed characteristics of reduction in periodontal pathogens (*P. gingivalis*: 0.32 vs. −1.10; *F. nucleatum*: 0.43 vs. -.1.55; Control vs. Test group with probiotics). Additionally, the composition of the microbiome significantly differs between individuals and the pooled mean usually yields more pronounced standard errors. One must consider if the sample size has enough power or whether various factors that might impact the microbiota are well-adjusted in the study design. Strategies to enhance the adherence and colonization of the probiotics is also under development.[9]

In addition, there may be multiple strains of bacteria that can serve as probiotics, and current product mostly includes various bacteria as a hybrid product. It is likely that multiple strains of probiotics may best exert synergistic effects, but this also cause future research very difficult to dissect individual impact within the microenvironment. Each patient also has different oral immune response and tolerance, which also call for personalized precision medicine. Before we have the technology and resource to navigate the complexity of host-microbe interactions, certain strains of probiotics have emerged as a potential aid to enhance the outcome of non-surgical treatment. Future implementation of adjunctive probiotics in the comprehensive periodontal treatment is expected, and the opportunity to initiate host modulation therapy for contemporary patient care.

Declaration of competing interest

The author has no conflict of interest related to this article.

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