The microbiome, an interfacial relationship between general and oral health

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Decades of recognition underscore the critical importance of optimal dental care for sustaining oral health. The interplay between diseases like dental caries, periodontitis, and peri-implant inflammation, and their impact on overall health, has been a concern for over seventy years. This connection, driven by systemic dissemination of pathogens from oral biofilms, disturbed homeostasis, and inflammatory mediators, underscores a significant relationship between oral and systemic health. With tooth loss statistically linked to life expectancy, addressing orointestinal dysbioses and promoting immune homeostasis becomes paramount in preventing non-communicable diseases. Enhanced interdisciplinary collaboration between dentists and physicians is essential for achieving this goal, thereby ushering in a new era of preventive healthcare.

Since many decades it has been widely recognized that establishment of optimal dental care is of paramount importance for guiding and maintaining oral health. The relationship between diseases relating to oral biofilm such as dental caries, periodontitis and, more recently, peri-implant inflammation and moreover, the relating reciprocal impact relevant to diseased states pertaining to remote organs, have been of concern to medicine for more than seventy years [1].

The connection between oral and systemic diseases is based on systemic dissemination of pathogens stemming from oral biofilms (via haematogenous, oro-digestive, oro-pharyngeal routes and even by neuroinvasion), a disturbed redox- and cytokine homeostasis (including cytokinemia and other inflammatory mediators present in circulation), the myelopoiesis training status of bone marrow, age-related progressive accumulation of harmful biomolecules in the body and gene regulatory changes. These are all factors in a process leading to progressive damage in functionality of the human body resulting from an aging-related constitutive, bodily total inflammatory burden (referred to as systemic chronic inflammation, SCI), summarized under an umbrella term "inflammaging".

Statistically, there is a significant connection between tooth loss and life expectancy. Increased mortality rates have been reported in patients with severe periodontitis. A crucial correlation in this regard is the state of the orointestinal microbiota consisting of a total of 20 trillion microorganisms essentially encompassing a bacteriome, a mycobiome and a virome (including a phageome). It is important to distinguish between microbiota and microbiome. Microbiome is defined as the entirety of genetic material of vital and non-vital parts of the microbiota (including subcellular particles) within a specific environment, e.g. the orointestinal tract. Accordingly, the microbiota is an assemblage of microbes and the microbiome is a repertory of genetic material.

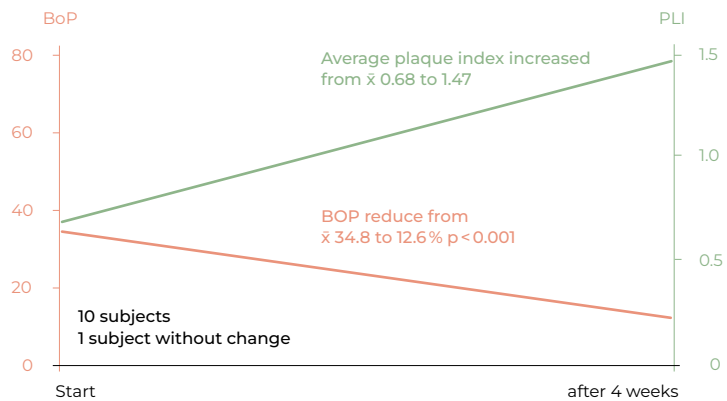
The microbiota should be in balance in terms of composition, species diversity and gene richness, thus promoting immune homeostasis and neurohomeostasis, extremely crucial for prevention of non-communicable diseases (NCD). The developmental und functional framework is nature-given through coevolution of orointestinal tract, enteric nervous system, mucosal immune system and microbiota in circumstance peaceful over many millennia, due to presence of enormous numbers of immune cells and neurons in the intestinal wall. Resulting host-microbe evolutionary interactions were as follows:

1. a reactive situation of the immune system characterized by physiological tolerance (toward harmless environmental stimuli and the body's own macromolecules (Fig. 5).
2. appropriate, sophisticated mechanisms for effective elimination of infectious and sterile noxious agents.

However, since the beginning of the industrial revolution, the entirety of all non-genetic, endogenous and exogenous environmental influences to which an individual is exposed throughout lifetime, the so-called exposome, has undergone sudden and drastic changes. This has led to the loss of numerous symbiotic microbial species (our "old friends") resident in most all humans just a hundred years ago, and in many cases the microbiota has also adopted a dysbiotic state, promoting loss of immunological tolerance and increase in systemic chronic inflammation (SCI). Other pathogenic factors of the modern lifestyle exposome also contribute to orointestinal dysbioses, which represent a basic etiological evil of modernity. One of the etiologic evils are xenobiotics present in environmental toxins, drugs (including vaccines and their adjuvants), biomaterials, nutritional noxious substances (including excessive consumption of refined sugars and fats, as well as food additives) and addictive substances (such as alcohol and nicotine).

FIGURE 1

Live as in the Stone Age – Swiss television, 2007
Inflammation index (BoP) & plaque index (PLI)
without oral care



The scientifically supported Swiss television program in 2007 followed ten people who lived as if they were in the Stone Age and, despite abstinence from hygiene, after four weeks they unexpectedly had healthier gums and fewer aggressive bacteria despite higher accumulations of dental plaque. The connections are shown in the book: Oral Preventive Medicine by Sanderink/Renggli/Saxer [3].

Source: Baumgartner, Imfeld & Persson et al., J Periodontol (2009)

Experiment with "Stone Age Nutrition"

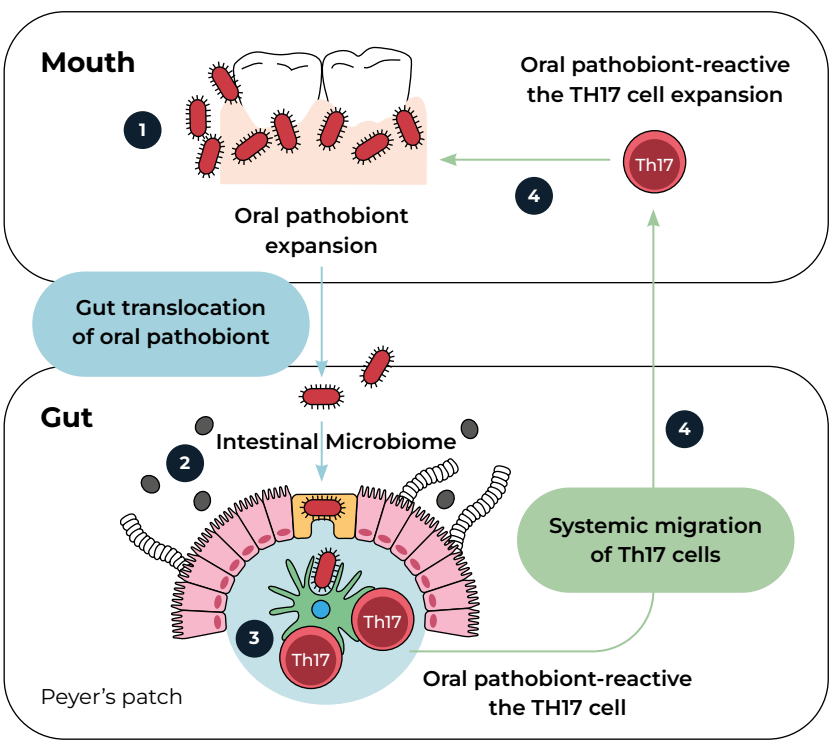
In 2007, a Swiss television program entitled "Living as in the Stone Age" scientifically supported by the Universities of Bern and Zurich presented astonishing discoveries. The study encompassed ten test subjects who were not allowed to clean their teeth with the usual hygiene products for four weeks. The study design resembled the end of a "Stone Age period" comprising, as far as possible, no immunogenic factors of the modern exposome. All subjects were given "Stone-age nutrition" in an environment without modern everyday life stress, which demonstrated stunning results including significantly less inflamed gums and, in comparison to the previous microbiotic burden, a significant reduction in pathogens (Fig. 1) [2].

Statistically, there is a significant connection between tooth loss and life expectancy.

At the time, these results were almost incomprehensible. Subsequent international research projects revealed circumstances in caries and periodontitis, where very high numbers of pathogens from dysbiotic oral microbiota were swallowed in large quantities, especially during main meals (Schmidt et al. 2019) [4]. For example, 1 ml of saliva from a patient with severe periodontal disease possibly contains more than 10^6 colony-forming units of the inflammatory pathobiont Porphyromonas gingivalis. In fact, subjects suffering from periodontal disease swallow 10^8–10^{10} of these keystone pathogens, being characterized as capable of exerting pathogenic effects even in very small quantities.

FIGURE 2

Development of severe periodontitis via Gastro Intesteinal Tract (GIT)



In the event of an infection (Dysbiosis) the Th17 cells (helper lymphocytes) move from the gut to the mouth and worsen the periodontitis.

***Porphyromonas gingivalis* (Pg) penetrate the intestine, where they activate proinflammatory Th17 helper cells, which in turn are transported via the bloodstream into the periodontal tissues where they aggravate inflammation.**

Fig. Summary, Nagao, Kishikawa, Tanaka et al. Bioscience / Cell Press, 2022

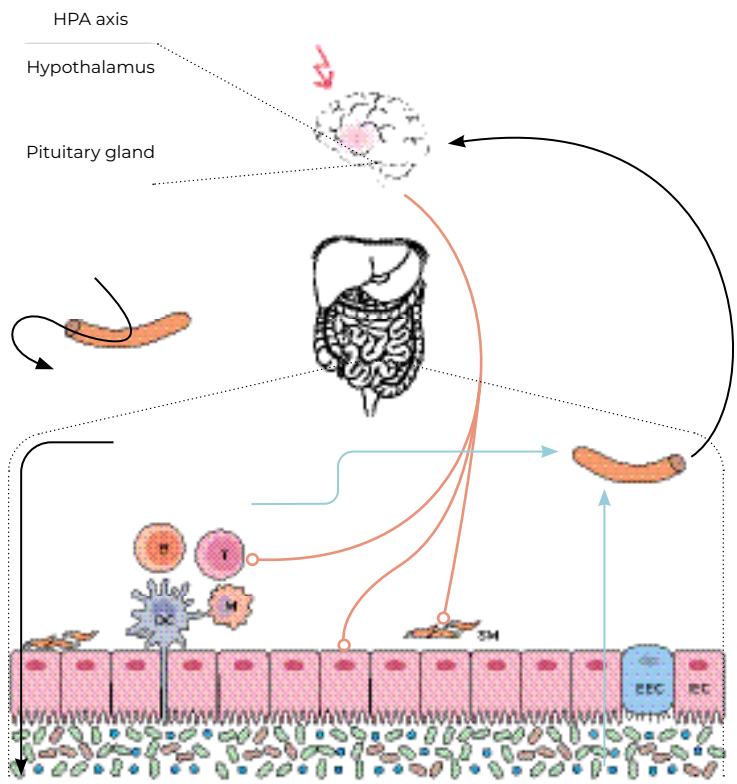
Microbes swallowed survive a temporary increase in pH values in the stomach – immediately after a meal values are approximately pH 5 – and also resist antimicrobial bile acids in the duodenum. Upon further voyage into the intestinal tract, microbes become operational "dysbiotics", contributing to a loss in microbial homeostasis. Orointestinal dysbiosis results in a pathological increase in permeability of mucous membranes and periodontal/periimplant epithelial tissues conferring a transfer of microbes including their virulence factors into lymphatic and blood vessels. Finally, a predominantly gram-negative, dormant blood microbiome with endotoxinemia can be established, representing an immunogenic trigger factor (Fig. 2). Moreover, in Peyer's patches oral pathogens elicite the differentiation of naïve T cells into proinflammatory T-helper cells which, in turn, migrate per hematogenem into the mouth, thereby promoting inflammation of periodontal tissues (Nagao et al. 2022) [5].

P. gingivalis also perturbs innate immune responses, thereby significantly increasing their survival in infected tissues. Thus it is not surprising that *Porphyromonas gingivalis* (Pg) is frequently detected as a dominant pathobiont in a wide variety of sites throughout the body, such as arteriosclerotic vessels, infected joints and rheumatoid arthritis; *P. gingivalis* is also overall predominant in obese constitutions. Pg leads to impairment of glucose metabolism through disruption of insulin signaling pathways (thus decreasing insulin sensitivity), induces hypofunction of pancreatic beta-cells and reduction in specific cell population and accordingly, contributes to insulin resistance, as precursor of diabetes. Even fetal tissue becomes adversely affected by this pathogen. Based on these findings, it is also clear why this KEYSTONE pathogen was named ***P. gingivalis***, as its pathology was discovered by oral microbiologists early in the 1980s. However, the ***bacterium*** not only develops its pathogenic potential in periodontia, but also destroys other tissue structures.

In addition to food, swallowed bacteria and oral antibiotics, endogenous factors of the exposome, such as psychological influences and stress (the latter via the so-called gut-brain axis, DHA) can have a significant impact on the orointestinal microbiota and thus on immunity, including development of NCD and also on health, in general. Conversely, intestinal dysbiosis disrupts the DHA-homeostasis, which may elicite behavioral changes, cognitive impairment and altered pain perception (Fig. 3).

FIGURE 3

Bidirectional communication between the gut and the brain



Bidirectional communication between the gut and the brain (gut-brain axis= GBA). This simplified representation demonstrates neuronal connections (mainly via N. vagus X) and humoral communication pathways (hormones, immunological messengers, neurotransmitters).

ACTH = adrenocorticotropic hormone; B = B lymphocyte; CRH = corticotropin-releasing hormone; DC = dendritic cell; EEC = enteroendocrine cell; SM = smooth muscle; HPA axis = hypothalamic-pituitary-adrenal axis; IEC =intestinal epithelial cell; M = macrophage; SCFA = short chain fatty acids; T = T lymphocyte.

Image: R.B.A. Sanderink

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Interdisciplinary collaboration

Conjecturing a future professional medical environment, medical disciplines must be viewed holistically, and the mouth must be "put back into the body". Therefore, the next challenge absolutely necessary for implemention is an intensified interdisciplinary exchange between dentists and physicians. This collaboration also affects psychiatrists, psychologists, educators, coaches, managers and, in short, everyone who takes on responsibility for human beings [3].

The most important clinical task is to establish microbiomes with dysbiosis-resistant phenotypes in future offspring through structured collaboration, particularly between dentists, gynecologists, general practitioners and internists. Having this main goal in mind, an interdisciplinary cooperation should be initiated and established during the perinatal period, from the beginning of pregnancy up to one year post-partum. One example to illustrate positive outcome: After a perinatal intake of probiotics, a good immune defence remains observable in these offspring decades later, especially in the form of a dysbiosis-resistant indigenous microbiota. When pregnant women take probiotics during the perinatal period and, accordingly, newborns receive mother's breastmilk and also probiotics through administration during the first year of life, a reduction in incidence of caries of over 50%, gingivitis of over 40% in children aged 10 years could be registered (Fig. 4). In addition, eubiotic orointestinal microbiomes promote better physiological development of nervous system and immune system combined, in childhood. For general medicine, this means a significant elimination and/or reversal of SCI, lowering clinical susceptibility to non-communicable chronic inflammatory diseases such as cardiometabolic and neurodegenerative diseases, autoimmune diseases, cancer, allergies, and even psychological disorders [3,7].

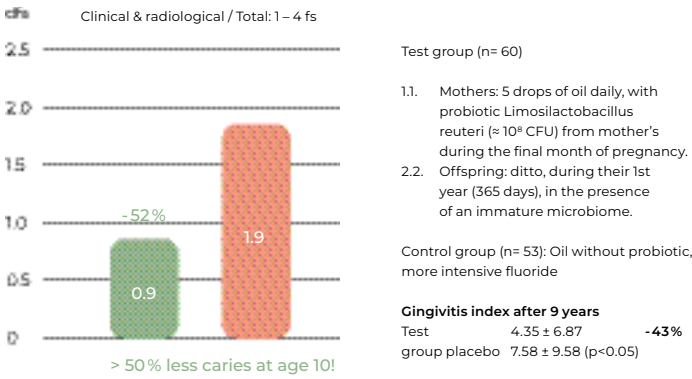
The role of the dental clinician is very special in that they are medical professionals uniquely, for the most part, seeing a majority of the population for a regular, once a year check-up. In this respect, regular monitoring of the development of each patient case history, documentation of oral microbiome homeostasis while, as far as possible, employing noninvasive interventions to evade an increase in xenobiotic burden. Hereby, the dental clinician is capable of early recognition, detecting signs of NCD, such as gingival inflammation, oncoming obesity or dementia, which should subsequently be referred to a family doctor, psychiatrist, etc. to reverse the course of NCD (Fig 5).

Summary and recommendation

During the past fifty years the dental profession has succeeded worldwide in many fields of oral prevention, medical and technical, especially caries, periodontitis and oral NCDs. Since such an achievement was possible in dentistry, a corresponding interdisciplinary success should also be possible in general medicine to the benefit of the population as a whole through increased interdisciplinary collaboration: NCDs such as diabetes, autoimmune diseases, arteriosclerosis, cardiopathy, related circulatory diseases, neurodegenerative diseases (Alzheimer's & Parkinson's) and mental disorders (such as autism) could also be markedly reduced! However, this also requires changes in university curricula and professional networks. Political authorities, health economists, educators, nutritionists and superiors are also on call for duty.

FIGURE 4

Caries and gingivitis in 9-year-old children



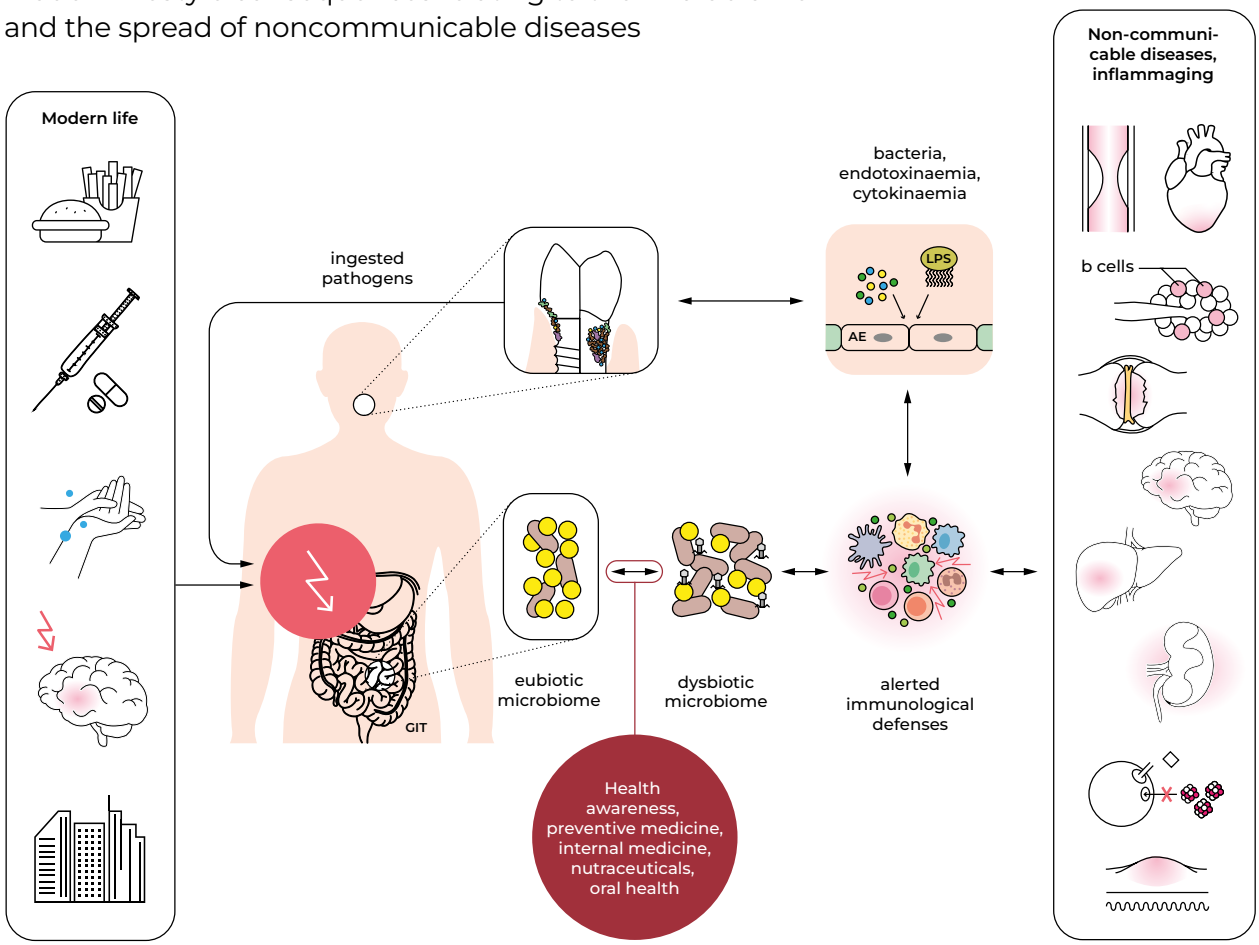
All of the children over two years of age demonstrated through unsupervised developmental randomization in double blind trials, statistically highly significant results

d = decayed by grades 1–4, f = filled/s=surface

In this experiment, the mothers took 5 drops of oil with probiotic Limosilactobacillus reuteri every day four weeks before the birth (to get used to it). The infants/toddlers received 5 drops of oil containing probiotic Limosilactobacillus reuteri or a placebo oil daily from their mothers during the first year of life. The children's caries and other parameters (gum inflammation) were examined in a blinded manner shortly after the age of nine (Stensson et al. 2014) [6].

FIGURE 5

Modern lifestyle consequences relating to the microbiome and the spread of noncommunicable diseases



Graphical summary of the book content [3,7]. The relationships between today's life, the occurrence of NCD, SCI and inflammaging are depicted, as well as the role that the microbiome, the immune system and the nervous system play here. Curative and preventive interventions require interdisciplinary collaboration between oral medicine and general medicine.

AE = activated endothelial cell; GIT = gastrointestinal tract; LPS = lipopolysaccharide; NCD = non-communicable diseases; SCI = systemic chronic inflammation

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