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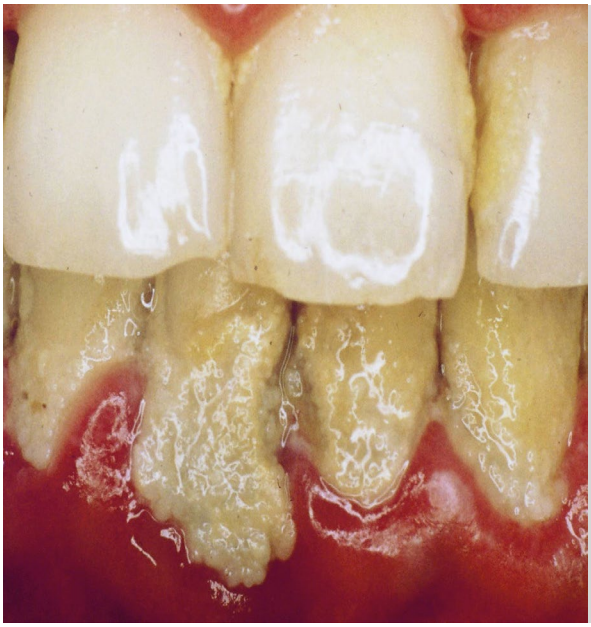
Oral Dysbiosis and General Diseases

Part 1 – Etiology and therapeutic significance



Quintessence for the practice team

Periodontitis is the result of subgingival dysbiosis, a disturbed equilibrium in the biofilm. On the one hand, a dysbiotic biofilm represents a risk factor for endocarditis and pneumonia. While on the other hand, a periodontitis is a risk factor for a number of systemic diseases. These include type 2 diabetes, cardiovascular, respiratory and neurodegenerative diseases, and cancer. Patients with type 2 diabetes derive significant benefits from periodontal treatment. Conversely, some systemic diseases can also affect oral biofilm-induced diseases. Accordingly, affected patients will require close interdisciplinary cooperation with internal medicine and other specialties.

Summary

Oral dysbiosis can be described as a pathological change of the microbiome with complex links to the immune response. This paper describes current concepts for the transition from a symbiotic to a dysbiotic state and its role in oral diseases, with particular reference to periodontitis. It also identifies important "general" diseases associated with oral dysbiosis and chronic inflammation. Finally, it provides information about the therapeutic effects of oral dysbiosis management on these diseases.

The oral microbiome as an ecosystem

In its healthy state there is an equilibrium between the microbial biotope and oral tissue (1, 2). This is partly symbiotic in that it is beneficial to the microorganisms and also to the host. For example, this applies for a reducing effect on nitrate, which has been confirmed for bacterial species from the Neisseria, Actinomyces and other genera.

The resulting nitric oxides inhibit inflammation and promote cardiovascular health (3). Specific microbiome "ecotypes" are also compatible with oral health compared to others and help to maintain its stability (4, 5).

A healthy microbiome (eubiosis) changes into a pathologically altered microbiome in the event of illness, and establishes a so-called dysbiosis (Fig. 1) (1). This can be associated with a number of factors or be caused by these (etiological link).

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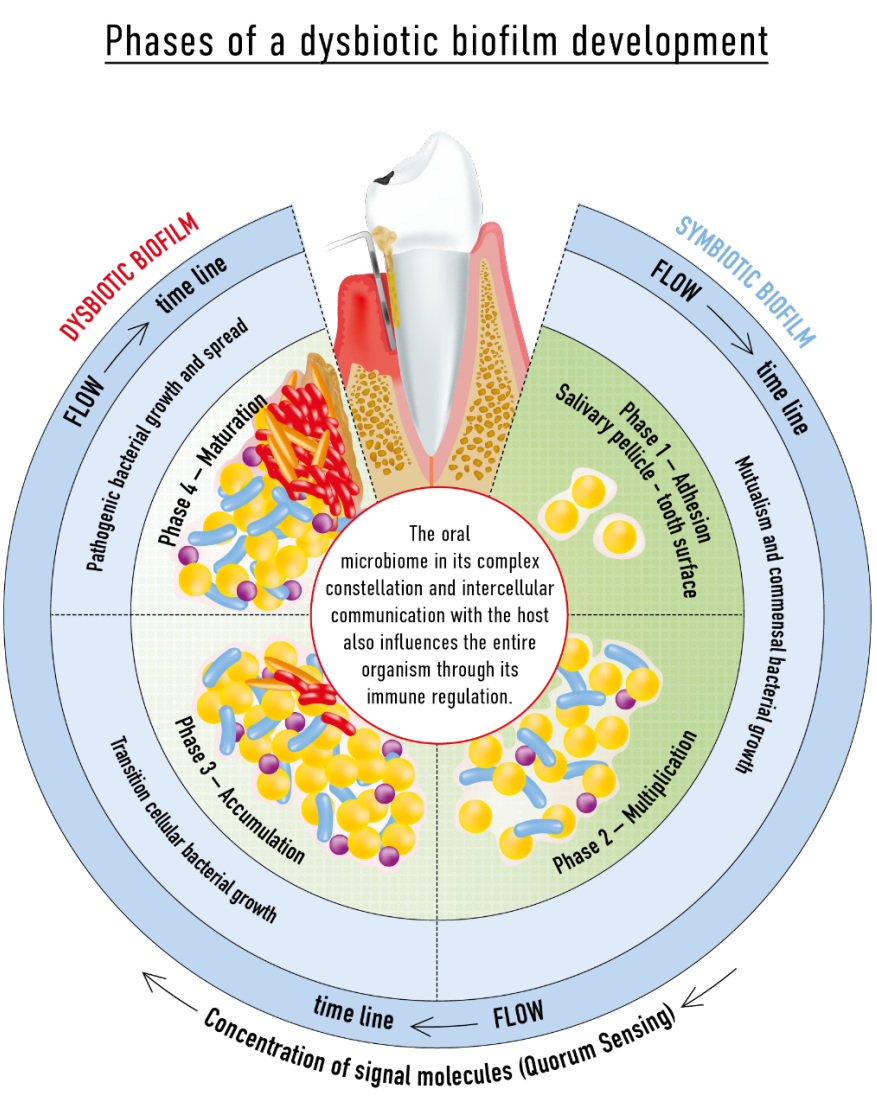

Fig. 1: Phase progression of pathological biofilm development: The transition to a dysbiotic microbiome only occurs when risk factors are present. These include poor oral hygiene, smoking, poor nutrition and systemic diseases. (Graphic: EMS)

These include poor oral hygiene, an unfavorable diet, hormonal changes resulting from pregnancy, insufficient or poor-quality saliva, smoking, stress, systemic diseases and antibiotic medication (4, 6-11). The role of genetic factors is still largely unclear (12, 13).

Summary: A pathological oral microbiome (dysbiosis) is caused or exacerbated by poor oral hygiene and other risk factors.

Dysbiosis and oral diseases

With regard to caries, a current prospective study using molecular biological analysis methods (next-generation sequencing) shows dysbiotic changes up to three years before the onset of a lesion (14).

The transition to a pathological condition therefore occurs long-term, and not, as previously assumed, due to short-term changes, for example in diet or oral hygiene. The underlying molecular biological relationships are still insufficiently understood (15).

However, in the case of gingivitis, there is an increasing volume of data on microbial and also immunological changes in the tissue (12, 16). With the potential transition to periodontitis, the equilibrium between microbiome and host response is pathologically disrupted, which results in inflammatory breakdown of hard and soft tissues (17, 18).

The time periods for the transition to dysbiosis are probably individually different and dependent on risk factors (see above). Here too, based on findings from therapy, longer periods can be assumed that differ prior to the initial manifestation of periodontitis and in supportive periodontal therapy (SPT) (19).

A causal relationship is also suspected between dysbiosis and the occurrence of oral squamous cell carcinomas. A retrospective study showed both to be independent of co-factors such as smoking and alcohol (20). A systematic review of the role of oral hygiene quality in patients with head and neck carcinomas provides further evidence for etiological links (21).

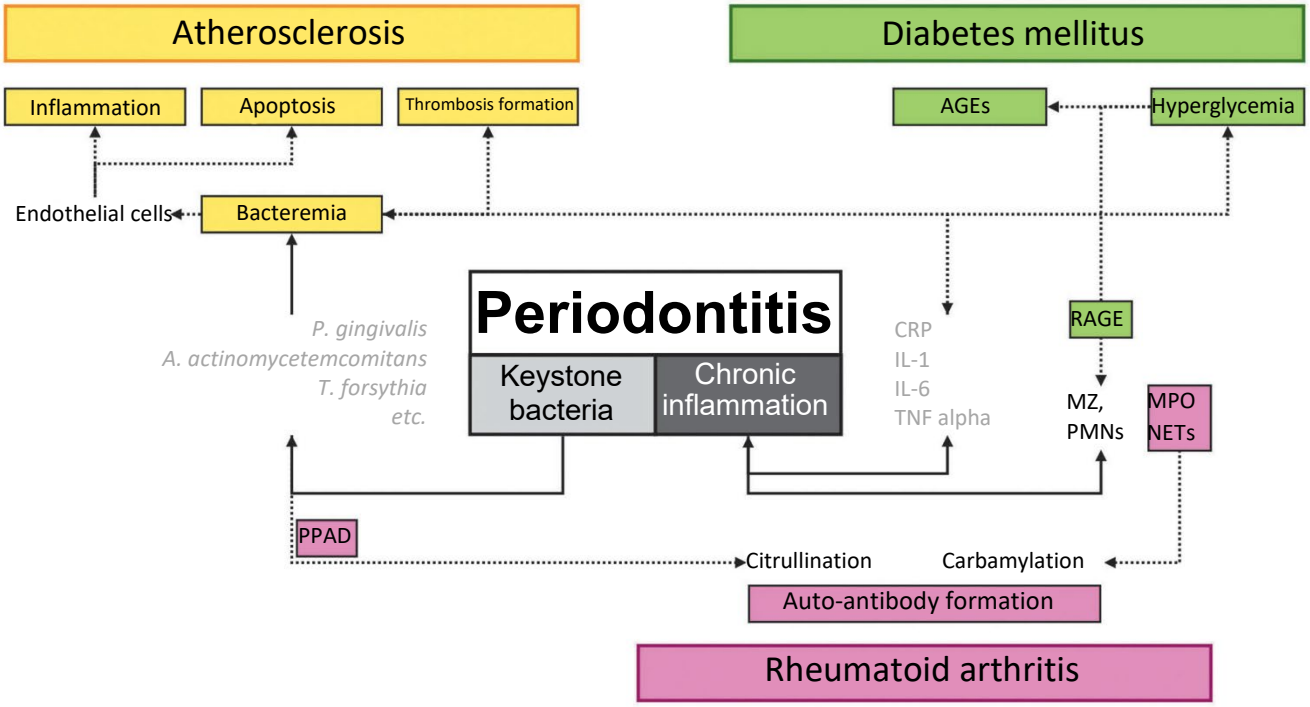

Fig. 2: Schematic view of interactions between periodontitis and the systemic diseases atherosclerosis, diabetes mellitus and rheumatoid arthritis
Explanation of abbreviations: AGEs/RAGE = glycemic metabolic products/receptors; CRP/IL-1/IL-6/TNF alpha = inflammatory mediators; MZ/PMNs = "scavenger cells" of the immune system; PPAD/MPO/NETs = relevant for the formation of autoimmune antibodies (diagram originally published: Dommisch H, et al. Parodontologie 2020, Volume 12, P. 1398) (74)

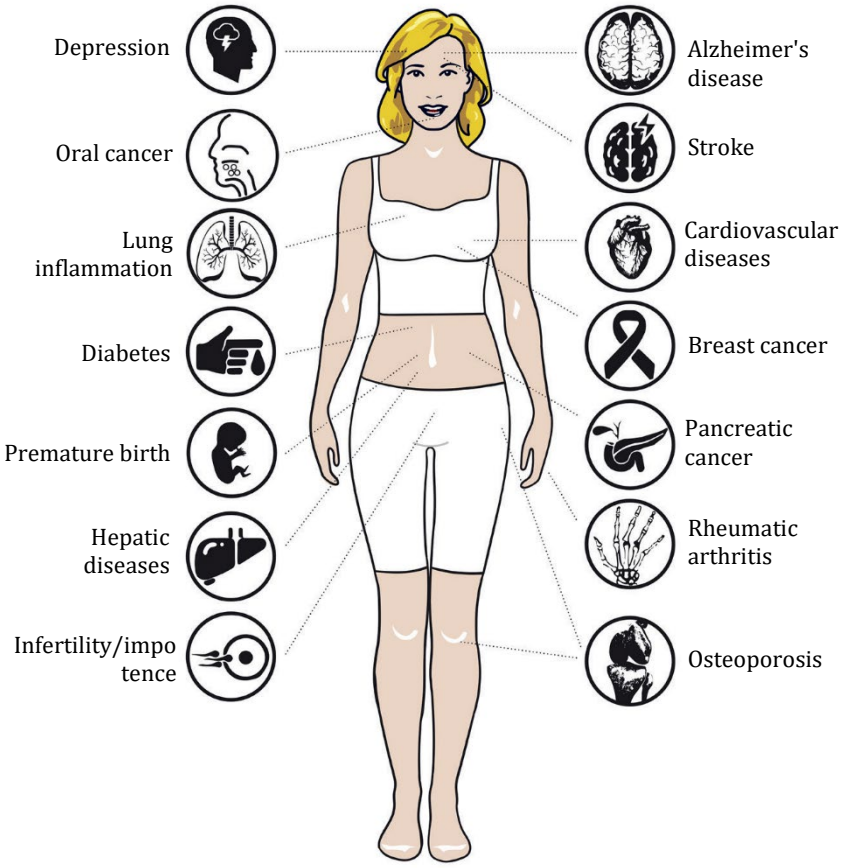

Fig. 3: A number of general and systemic diseases have been linked to oral dysbiosis and, in particular, with periodontitis. Causal relationships have only been clarified for some of them. (Graphic: EMS)

The microbiome on the surface of diseased tissue also differs between patients with squamous cell carcinomas and healthy individuals (22). However, a characteristic microbial composition in diseased patients could not be identified, so that the findings are not yet diagnostically useful.

Summary: *Caries and periodontitis are likely to be a consequence of specific, long-term microbial shifts. Squamous cell carcinomas also have an altered microbiome.*

Oral inflammation as interface

The interaction between microbiome and inflammation is considered to be a decisive etiological factor not only in oral but also in many other chronic inflammatory diseases in the body (23, 24). Thus, mechanisms are increasingly being described that link periodontitis, for example, with cardiovascular diseases, diabetes or cancer (25-27). Via the bloodstream (bacteremia), microorganisms and inflammatory mediators from the inflamed area of the body enter the bone marrow, where they not only trigger a local innate immune response but also an adaptive (acquired) immune response (28). This occurs over extended periods, plays a central role in chronic diseases and also results in an increased tendency to inflammation even when periodontitis has been treated (29, 30).

Depending on the severity of the disease, the large surface of inflamed tissue in periodontitis promotes these processes (31). They could represent an etiologic link between oral and systemic diseases and explain the frequently "shared" prevalence (25). However, depending on the disease, it is still unclear whether the inflammation in the oral cavity is an independent etiological factor or whether it is a non-causal coincidence (association) in the sense of a generally increased propensity for inflammation in the body. A causal relationship can only be reliably demonstrated with interventional studies, ideally with well-conducted randomized controlled trials (RCTs). These are usually required by reimbursers before approving new insurance benefits, but they are complex and can be difficult to implement from an ethical point of view.

Summary: *Chronic inflammatory diseases in the mouth and the rest of the body have common immunological features. They could be an etiological link that helps to explain a common increased prevalence.*

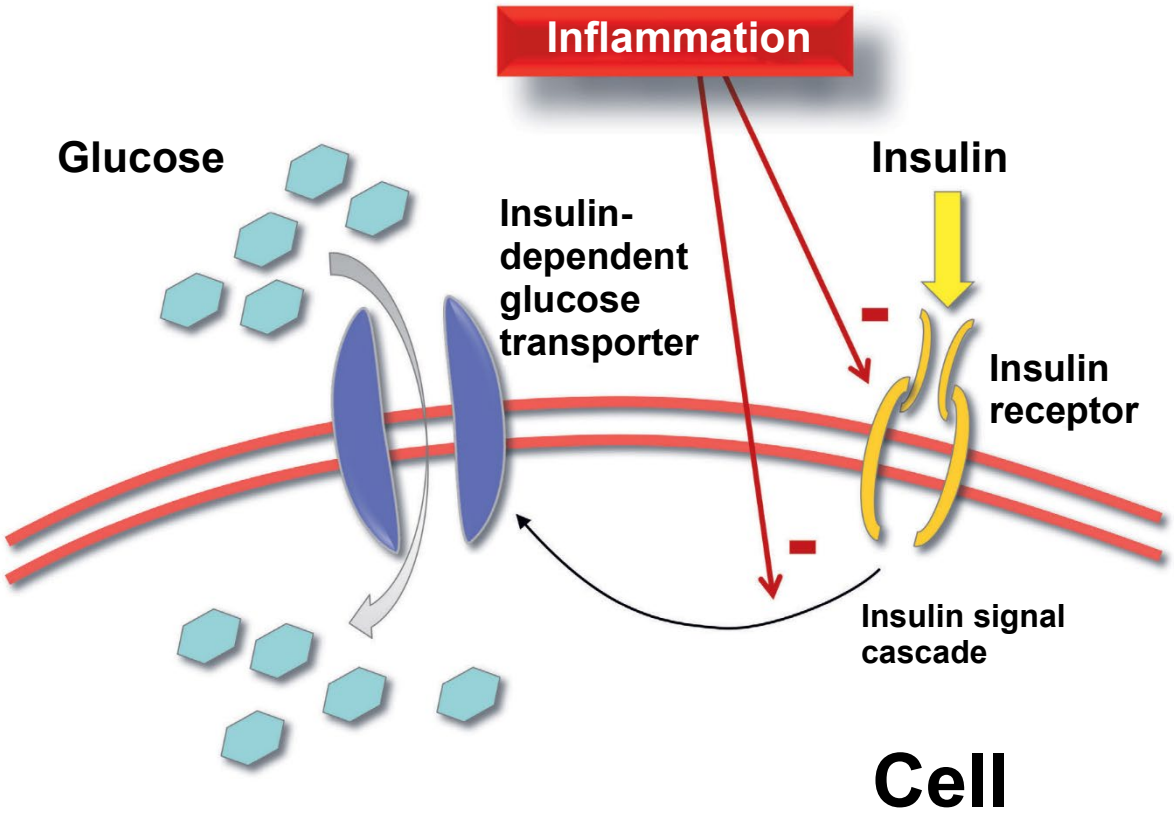

Fig. 4: Inhibition of glucose uptake by inflammatory mediators: These can inhibit insulin resistance by, among other things, activation of the insulin receptor. This prevents the insulin-dependent glucose transporter from being incorporated into the cell membrane. (Diagram: James Deschner, zm 98;2008(18):28-40) (74)

Oral and systemic diseases – clinical evidence

A current joint consensus statement by the European Federation of Periodontology (EFP, science) and the European branch of the World Organization of Family Doctors (WONCA Europe, professional association) defines type 2 diabetes, cardiovascular symptoms (e.g. high blood pressure) and chronic obstructive respiratory diseases as "independently associated with periodontitis" (32). A systematic literature review from 2022 further states that successful periodontitis treatment reduces "cardiometabolic" risks and systemic inflammation (Fig. 2) and results in fewer premature births (33).

Altered inflammatory marker and blood glucose values served as indicators for the first two points. In the RCTs evaluated for this purpose, however, only periods of a maximum of six months were examined. Clinical endpoints for cardiovascular events, such as myocardial infarctions or strokes, which usually occur after longer periods of time, could not be included. The following is a discussion – without claiming to be complete – of some diseases and disease complexes that are associated with oral dysbiosis in various ways or for which a link is discussed (Fig. 3).

Cardiovascular diseases and diabetes

A cardiological guideline recommends a clean mouth and if necessary periodontal therapy as prophylaxis for endocarditis (34).

With reference to cardiovascular diseases a Cochrane review in 2019 with rigid criteria along with a newer systemic overview concluded that periodontitis is not confirmed as a causal factor based on the available clinical studies (35, 36). However, systematic overviews and an interdisciplinary consensus paper published by European professional associations already recommend good oral hygiene and therapy of a manifest periodontitis to exclude risk factors (36, 37).

A systematic evaluation of the literature for secondary diabetes (type 2) shows that periodontal therapy results in "clinically relevant" improvement of the glucose value (HbA1c) after six months (38). In contrast, periodontitis¸ as previously suspected from the early 1990s, can be viewed as a "diabetes complication" requiring treatment (Fig. 4) (39).

Therefore, the probability of success of periodontal treatment is reduced in the presence of poorly controlled diabetes (40, 41). Interdisciplinary consultation with the internist or primary care physician is indicated for both disease groups (32).

Summary: *Long-term data for the efficacy of periodontitis therapy for systemic diseases are still rare. The same applies also for cardiovascular diseases and diabetes, where the study situation for diabetes is more robust.*

Pregnancy and birth

Statistically weak, but independent of other risk factors, correlations were also found between oral health and adverse course or outcome of pregnancies (42). Infection of the fetus or embryo with pathogenic microorganisms via the placenta is one of the subjects under pathogenetic discussion (43). A therapeutic effect of gingivitis or periodontitis treatments has been shown, albeit with only weak evidence, for premature births and reduced birth weight (44, 45). As with cardiovascular diseases, good oral hygiene and professional prophylaxis – and, if necessary, periodontitis treatment – are recommended for reducing risks, ideally as much before birth (46, 47).

Respiratory diseases and Covid-19

Associations of respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), have also been associated with periodontitis (48). The risks of infection and mortality are found to be increased for Covid-19 patients with periodontitis (49, 50). Additional etiopathological links between the oral cavity microbiome and acute and chronic pulmonary diseases are also being discussed (51). There are also only limited intervention studies in this field with limited data that indicate a positive periodontal therapeutic effect for COPD, OSA and asthma (52).

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Professional oral care treatments or prior periodontal treatments can also be implemented to prevent aspiration pneumonia in hospitalized patients (52-54).

Summary: *Good oral hygiene and if necessary periodontal therapy is indicated to prevent complications in connection with pregnancy and birth. Limited evidence supports the same measures for patients with manifest or increased risk of pulmonary diseases.*

Rheumatoid arthritis and neurodegeneration

Rheumatoid arthritis (RA) is an immunological disease that manifests with swollen and reddened joints and is linked to an increased risk of periodontitis (55). An increased immune response in RA patients to the key periodontitis organism Porphyromonas gingivalis and a reduced activation of T-killer cells (56). A systematic overview shows reduced RA disease activity as an effect of periodontitis treatment (57). Conversely, RA therapy with medication can counteract periodontitis inflammation (58). Interdisciplinary consultation is also recommended in this case as with other diseases mentioned in this paper (59).

An additional complex with reference to periodontitis includes neurodegenerative and dementia diseases such as Alzheimer and Parkinson. Animal studies in diseased tissue point to a pathogenic role for oral microorganisms (60, 61). A cross-sectional study with large patient collectives indicates a connection between periodontitis and changes in the white brain substance (62). Observational studies indicate a connection of stress and depression with gingivitis and periodontitis (7, 63, 64).

In this case, and also with caries, the etiological result may be a reduced immune response to microorganisms and thus associated pathological changes in the form of a dysbiosis. However, this assumption must be examined with reference to distortion factors such as stress-related changes in nutrition or oral hygiene (63).

Summary: *A bidirectional therapeutic benefit is shown for rheumatoid arthritis, which supports the use of interdisciplinary cooperation. Different types of links to oral diseases are also documented for neurodegenerative diseases, stress and depression.*

Oncological diseases

The etiological role of microorganisms in oncological diseases is well documented, for example with reference to stomach cancer (Heliobacter pylori) and cervical cancer (papillomaviruses). Analogous to the development of oral squamous cell carcinomas, microorganisms spread from the mouth through the esophagus, trachea or through the blood can also cause or contribute to a pathology in the rest of the body (65, 66). Suspected species include Fusobacterium nucleatum and Porphyromonas gingivalis, both of which are also significant in periodontitis (67). As described in the "Oral inflammation as interface" section, microorganisms can be involved in the genesis of cancers by immunological processes (30, 65, 68). In some cases, large-scale epidemiological studies give contradictory results with reference to a correlation between periodontitis and the incidence of cancer (69, 70).

Regardless of this question, oncological patients under immunosuppression should pay close attention to oral hygiene and periodontal health prior to treatment (53, 71). This would also include professional preventive support throughout the course of treatment for the disease (72).

The same treatment is also strongly recommended for patients with squamous cell carcinomas in the oral and tracheal regions (73).

Summary: *The role of oral microorganisms in the development of cancers is still not sufficiently studied. Immunosuppressed oncological and other patients should receive preventive treatment at an early stage.*

Conclusions

Dysbiosis as a pathological shift in the microbial equilibrium in the mouth is a significant risk factor for oral diseases and also for diseases in the rest of the body.

The same also applies not only to the currently best researched cardiovascular diseases and diabetes mellitus but also to many other diseases, including oncological. Successful treatment of patients requires comprehensive knowledge of their medical history, other risk factors and if necessary professional interdisciplinary consultation.

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Conflict of interest: The author has been contributing articles and consultation services to EMS and Philips for many years.

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