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Oral microbiota and systemic disease

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ABSTRACT
The oral cavity is has been resided by thousands of species of microorganisms, which remaining in different relationships. Disturbing the balance between microorganisms and host immunity can lead to the development of many serious local conditions, as well as changes in the organs placed away from the head and neck region. This article describes serious complications of local oral cavity infections like - exacerbation of chronic obstructive pulmonary, brain abscesses, infective endocarditis, diabetes mellitus, and even sepsis. The article also shows the potential connections between periodontal tissue inflammation and neurodegenerative disorders or cancer placed in distant organs. During treatment of periodontal patients, the physician should remember about the influence and risk of bacterial oral diseases.

Key words: oral microbiota, systemic diseases, oral cavity health, diabetes, infective endocarditis, brain abscess

INTRODUCTION
The oral cavity is a complex environment, full of microorganisms: bacteria, fungi, viruses and even protozoa and archaea. Commensals have got protective function against colonization of extrinsic bacterias, which may be causative agents of dangerous diseases. The

correct relationship between others microorganisms and the balance between microbiotas and the body's immune system affect the health of the entire organism (1,2,3,4).

Microbiotas in humans' oral cavity attaches to multiple surfaces like tooth, mucosa or tongue surfaces. These endogenic organisms on teeth surfaces (under and above the gum line) form dental plaque - an organized structure, which consists of bacteria and their metabolic products. The dominant genus isolated from the dental plaque is *Streptococcus* (*S. mutans, S. mitis, S. gordonii, S. sanguis*) (5,6). Those acidogenic bacteria, contribute to the damage of the enamel due to their acidic metabolites, which makes them causative agents of caries (7). Other species isolated from dental plaque include *Campylobacter, Actinomyces, Capnocytophaga, Veillonella, Fusobacterium* or *Neisseria* (3,8,9,10). In the process of calcification, plaque remodels into tartar.

Accumulation of a dental plaque and calculus inflame periodontium - gingiva, periodontal ligaments and alveolar bone (5). Periodontitis is a complex, biofilm-inducted disease, which is strongly connected with the immuno-inflammatory response of the host (5,11). Prevalence of this condition in the US is estimated above 47% of adults. Bacteria associated with periodontitis include *Tannerella forsythia, Porphyromonas gingivitis,* and *Treponema denticola*. Also, *Aggregatibacter actinomycetemcomitans* induces destructive inflammatory host response. The newest model of this disease, suggest as a cause rather dysbiosis and polymicrobial synergy between microbiota than the occurrence of the individual pathogen (5,11). The development and progression of periodontitis are modified by genetic, mechanical and environmental factors. Periodontitis results in the destruction of tooth-supportive structures (periodontium).Inflammatory processes in the oral cavity, including periodontitis, may be associated with multiple systemic conditions (7).

Over 90% of head and neck infections are secondary to odontogenic infections, which may be initiated by caries, root cysts, periodontal disease, and other oral cavity disorders. The infectious agent may metastasize from the primary inflammation focus located in the dental areas, even to the distant organ causing therein pathological changes. These conditions can result in the formation of abscesses or connective tissue inflammation, while severe cases may even lead to death (12,13). If odontogenic inflammations are not properly treated, may cause serious pathologic processes in the fascial spaces, and etiological factors may spread all around the organism and lead even to sepsis (14).

ORAL MICROBIOTA AS CAUSATIVE AGENTS OF SYSTEMIC DISEASES

The literature abounds in many types of research confirming the relationship between odontogenic infections and some systemic diseases such as gastrointestinal, respiratory or cardiovascular diseases.

1.**Diabetes**

Hyperglycemia in diabetic patients causes recurrent decrease volume of the water in the organism and changes in the concentration of electrolytes in the various body fluids, among another saliva. That may lead to changes in the quality and quantity of saliva. The decrease the flow rate of resting and stimulated saliva predisposes to xerostomia. Also, the pH of the saliva under correct values. The reason for this condition may be degeneration of the salivary glands as a result of lipids deposition between the gland cells. These abnormalities lead to an increase in the incidence of caries and periodontal disease among patients with diabetes, especially those in whom the disease is not properly treated and glucose level is out of control. This fact was confirmed. among others, in research performed by *Seethalakshmi C. et al.,* (16,17).

Segura-Egea et al. studied the correlation between diabetes and the condition of the immune system. Correlations between diabetes with delayed healing and impaired immune

response, have been proved. That may predispose to increased activity of dental bacteria and lead to chronic inflammation of periapical tissues, progressive breakdown of bone tissue and reduced ability to repair damaged tissues. It is believed diabetes is a risk factor for increased gingivitis and periodontitis (18,19,20,21).

For the reasons mentioned above, diabetic patients may be more susceptible to cellulitis and deep neck infections as a result of odontogenic infections. *Ko et al.* performed a study using the Taiwan National Health Insurance Database (NHIRD) to analyze and investigate the correlation between diabetes and odontogenic infections among patients. The study analyzed 1 million individual NHIRD data sets from 2005. The results confirmed a positive correlation between cellulitis and patients with diabetes (15).

Ueta et al. studied the correlation between the prevalence of odontogenic infections and candidiasis on the incidence of diabetes mellitus. Researches also considered co-existing clinical symptoms of infections and neutrophil activity. 221 patients with mild and 21 with severe dental infection participated in the study. In each group, 5 of the patients were diagnosed with diabetes. However, from 64 patients with symptomatic candidiasis, hyperglycemia was detected in only 8 people. Moreover, among diabetics, both odontogenic infections and candidiasis healed worse due to neutrophil suppression. This research confirmed the occurrence of correlations between the examined individual diseases entity. However, it was not clearly stated that dental-derived infections or candidiasis can affect the incidence of diabetes (22).

2. Digestive system

Helicobacter Pylori (HP) is a Gram-negative bacteria that inhabit the surface of the epithelial cells of the mucous membrane of the effective margin of the stomach. Some of the studies suggest that HP may occur in the oral cavity and plaque. Infection with this organism can lead to gastritis, duodenitis, and in rare cases even to gastric cancer or MALT (mucosa-associated lymphoid tissue lymphoma) (27).

Zahedi et al., in their research discovered that HP-associated gastric infection occurred in respectively - 70%, 75% and 100% of patients with mild, moderate and severe DMFT (Decayed / Missing / Filled Teeth). On this basis, they concluded that there may be a connection between poor oral hygiene and pre-cancerous lesions of the stomach. In addition, HP infection diagnosed on basis of on gastric histopathology examination may be associated with periodontal disease. It is worth knowing that simultaneous treatment of periodontal diseases and gastritis can increase the rate of HP elimination from the organism (23,24). However, *Loster et al.,* compared the bacterial biofilm from the oral's cavity mucosa and from the gastric mucosa based on polymerase chain reaction (PCR). They presented the conclusion that oral bacteria and gastric bacteria are completely different, suggesting that *H. pylori* can only occur temporarily in the mouth and does not play a major role in *H. pylori* gastric infection (25).

Guzik-Cześnikiewicz et al. investigated the association of HP in the oral cavity and gastric. They confirmed the presence of bacteria in both - saliva and plaque. The presence of HP in the saliva of patients with teeth and toothless was also compared. They documented that the presence of teeth does not affect the presence of this bacteria in saliva. They did not find any significant association between HP presence in the stomach and oral cavity. Also, they suggest that the other factors, such as susceptibility to infection due to acidic pH in the stomach, may be the main reason for gastric infection with these bacteria - while in the oral cavity presence of this bacteria may be only a transient contamination associated with ingested food and without apparent impact on gastric infection (26).

3. Respiratory tract

From the external environment to the oral cavity is penetrated by bacteria such as *Actinomyces odontolyticus, Haemofilus influenzae, Mycoplasma pneumoniae, Staphylococcus aureus, Streptococcus intermedius or Streptococci viridans* (28). These microorganisms can invade the lower respiratory tract by translocation with air, saliva or blood vessels. The phenomenon of bacteria moving down the respiratory system is dangerous because it can lead to exacerbation of chronic obstructive pulmonary disease or pneumonia (28, 29).

In more severe cases, the infection can lead to the development of complications including abscesses or phlegmon (30). The case of the patient with lungs abscesses, caused by infection with the periopathogen A*ctinobacillus actinomycetemcomitans* (now *Aggregatibacter actinomycemcomitans*) was described by *Hagiwara et al.* Also infection connected with mentioned above periodontitis causative agent was described by Shilo et al. (31,32) As reported *Edno et al., Actinomyces* species, may be also cause of serious respiratory disorder - septic pulmonary embolism (SPE) (33).

The effects of periodontitis on chronic obstructive pulmonary disease are worth considering (34,35). *Porphyromonas gingivalis* is a bacterium found in pathological states of periodontitis. It can cause an increase in the pathogenicity of *Pseudomonas aeruginosa*, a bacterium responsible for the severe excerbration of chronic obstructive pulmonary disease. As a result of the mutual correlation of both bacteria, the apoptosis of epithelial cells is inhibited, and for a considerable time after the co-invasion of *P. aeruginosa* and *P. gingivalis*, a safe intracellular niche for these microorganisms is created, which allows multiplication and establishment of infection (5). It has been demonstrated that rapid apoptosis of infected epithelial cells contributes to the effective destruction of *P. aeruginosa* (36).

4. The nervous system

Alzheimer's disease (AD) and Parkinson's disease (PD), are the most common, chronic, neurodegenerative disease (37,38).

4a. Neurodegenerative diseases

AD prevalence increases together with age - from 4 to 19% of patients between 65 and 89 years old. It is believed that the disease is caused by the deposition of β-amyloid in brain cells. Probably, inflammation may be associated with the initiation and progression of the disease. Probably, inflammation may be associated with the progression and progression of the disease. Theory of inflammation, suggests that inflammation stimulate glial cells to produce pro-inflammatory cytokines (IL-1, IL-6, TNF). IL-1 and IL-6 stimulate the synthesis of A42 (A-amyloid 1-42 peptide) and P-Tau (phosphorylation of tau protein), whereas the above is capable of producing TNF and IL-1, IL-6 cells. That self-perpetuating processes may result with neurodegeneration (38,39). Also, other studies show that IL-6 and CRP are associated with an increased risk of AD (39). Gram-negative bacteria, activate the organism's cells to produce pro-inflammatory cytokines that, when crossing the blood-brain barrier, will affect the production of cytokines in the brain (38,39). The animal studies, performed on rats, proves that LPS, by cytokines, activate microglia. In the case of a long-lasting inflammatory reaction, were observed increment of TNF-α and IL-1 levels and amount of precursor of β-amyloid, also activation of astrocytes, which may result in pathological changes in the brain (40).

The mechanism neurodegeneration in PD is a loss of dopaminergic neurons in the brain, exactly in substantia nigra. It is suggested that some mediators (IL-1, IL-6, TNF- α), produced by host cells in reaction for bacterial LPS, may induce brain cells for producing

reactive nitric oxide and oxygen species which damages dopaminergic neurons (41,42). *Chen et al.,* performed a study on 4765 patients with PD and 19,060 non-PD patients. Research revealed that in next 5 years, non-PD patients, which regularly underwent dental scaling had a lover risk of developing PD (43).

Though, the connection between inflammation and the development and progression of Alzheimer's disease and PD is still debated. (37,38,39,40)

4b. Brain abscesses

Life-threating conditions, rarely caused by primary odontogenic focus are brain abscesses (BA). BA may be caused by many pathogens, among others those who occur in the bacterial flora of the oral cavity like *Fusobacterium, Actinomyces, Streptococcus or Prevotella.* (43,44,45)

Hibbed et al., described brain abscess in 11-years-old man, in which primary focus was a molar dental abscess (43). *Akashi et al.,* in case-series article present patients in who identified, pathogens were strongly connected with periodontal diseases - *Porphyromonas gingivalis* (1 case), *Fusobacterium nucleatum* (in two cases!) - none of those patients were diagnosed with acute inflammation of any teeth (44).

Brady et al., describe a case go 68-years-old woman with brain abscess secondary to the dental treatment. The causative pathogen, identified with molecular methods and found in the blood culture, was *Actinomyces actinomycetemcomitas* - a bacteria, part of endogenous oral cavity flora. This microbe is related to periodontitis, endocarditis, meningitis, and osteomyelitis. The patient's orthopantomogram (OPG) revealed numerous periodontal and caries affected teeth. The patient, during the treatment, underwent dental clearance of the oral cavity. The patient was treated with antibiotic therapy, surgical and afterward needed rehabilitation and physiotherapy (37).

The very serious case was reported by *Ben Hadj Hassine et al.*, 46-years old patient went craniotomy and received therapy consisted of multiple antibiotics due to brain abscess, connected with pathological changes of tissues surrounding two molars in the mandible (46).

5. Sepsis

The SIRS is defined as a systemic inflammatory response syndrome - and is diagnosed when proper clinical conditions occurs - like adequate temperature, heart rate, respiratory rate, or WBC (white blood cells) level in the serum (47,48). If the causative agent of inflammation is a microbe, we name it sepsis. Bacterial sepsis is a serious clinical condition, which develops in the patient as a reaction to specific integral parts of bacteria - such as lipopolysaccharide (LPS) - component of the bacterial cell wall. Their presence results in the secretion of appropriate inflammatory mediators (49). Severe sepsis is when the general infection, which affects organism, is accompanied by multi organs dysfunction. Sepsis has a high mortality rate (47).

Mostly, sepsis is caused by Gram-negative bacteria infection (57%), also often occurs Gram-positive bacterias (44%). Much rarer causative agents are fungi (11%). Patients with comorbidities like diabetes or cancer are more likely to develop sepsis (29).

The cervicofacial area is heavily vascularized, due to this fact infections may easily metastate to different, distant parts of the organism (29).

Van der Windt et al., described a case report of the 28 years-old patients, in which septicemia was caused by *Fusobacterium necrophorum* - anaerobic bacteria occurring in periodontitis. This patient was previously diagnosed with general periodontal disease. The important complication of the case is that the patient was pregnant, and in a result of an infection, she delivered the immature infant (50).

The Lemierre's (postanginal sepsis) syndrome is an uncommon, serious disease which mostly affects young adults - the sepsis, in this case, begins with an oropharyngeal infection, which spread. The etiological agent in most cases is *F. necrophorum* (50,51,52). Postanginal sepsis, in rare cases, may be also caused by Porphyromonas asaccharolytica (its role in periodontitis is still unknown)— like in the case described by *Mirudla et al*., (51). Also, *Garza-Alatorre et al.,* provide the extremely rare case of postanginal sepsis caused by Prevotella oris - a bacteria which is a part of normal oral flora. The 15-years-old male manifest among others headache, drowsiness, nausea and vomiting, right periorbital edema. The patient was hospitalized days after syndrome began, with suspected neuroinfection. W wywiadzie non-treated oropharyngeal infection three weeks ago. CT scan detected suspected mass in the right frontoparietal. Also, Doppler ultrasound examination was performed and revealed thrombophlebitis of the left jugular vein. Whats, more first 48 hours of admission patient developed septic shock and multiple organs failure. The patient was receiving multiple antibiotic therapies which consist of vancomycin, metronidazole, and ceftriaxone. Due to increased intracranial tension, a decompressive craniotomy was performed. Also, the patient underwent the lobectomy of a right lung lobe, due to persisting empyema. Fortunately, the patient survived (53).

6. Infective endocarditis

Infective ndocarditis (IE) is an inflammation of the internal heart tissue as a result of a bacterial infection (54). Data on the incidence of IE in the population are rare, according to The series of studies from 1960 to 2008 had a morbidity from 3 to 10 cases / 100,000 inhabitants (55). It is a row, but a severe disease with in-hospital mortality of around 20% (56).

IE is caused by adenoids that are composed by platelets and fibrin that firstly were considered sterile but might be colonized by microorganisms. The adhesion of bacteria to the endocardium depends, among others, from the ability of that microorganism to bind with the components of damaged endothelium (fibronectin, laminin, collagen). The progressive colonization of the coagulum causes adhesion of monocytes by the expression of IL-6, IL-8 and the chemotactic peptide, which increases the procoagulant cascade. As a result, more and more platelets are built into the aggregate (57). The risk factors are: damaged endocardium and bacteriemia (58). Causative agents are frequently bacteria, which occur in the oral cavity of patients with endocarditis. Dangerous pathogens include *Streptococcus spp.*, such as *S. sanguis*, *S. salivarius*, and *S. oralis.* Bacteria enter the bloodstream causing bacteremia as a result of dental procedures, even not invasive like brushing teeth or chewing food. Most often it affects previously damaged heart valves, usually mitral valve (54,58,59,60). Also, there is a risk of complications in distant organs, associated with a platelet-fibrin matrix that can travel to any organ and lead to an infraction. Other symptoms may result from the deposition of the immune complex. Multi-organs complications of endocarditis include:

- cardiac: inflammation may cause perforation of the valvular flap or rupture of the interventricular septum,
- glomerulonephritis (kidneys),
- Roth's spots - visible in the eye examination,
- Osler's nodes,
- splenic abscesses (57).

Patients with risk of endocarditis (after previous IE, congenital heart disease, palliative connections and other prostheses remaining as a result of the operation) should use an antibiotic prophylaxis for dental procedures at high risk of IE (28,54).

7. Cancer

The amount of evidence pointing to the link between periodontitis and gastrointestinal neoplasms is still growing. Such correlation is suggested with reference to malignancy tumors in the esophagus, stomach, colon, and pancreas. Periodontitis may be also associated with breast or prostate cancer (61,62).

Subgingival plaque pathogens strongly correlated with the development of periodontitis include Tannerella forsythia, Treponema denticola and Porphyromonas gingivitis. The host organism is not indifferent to the developing infection and infiltrates periodontal pocket with neutrophils, natural killers and granulocytes, what promotes inflammation. During inflammation, white blood cells release various types of cytokines which, through interaction with the appropriate cellular receptors, modulate cell behavior. Studies on *P. gingivalis* show that after absorption by a macrophage, it can affect its intracellular pathways, and cause secretion of cytokines. The mechanism linking periodontitis with carcinogenesis in distant organs can be triggered (in response to bacteria) by white blood cells. This bacteria modifies the effect of macrophages also by removing receptors, for example, P2X7 - which stimulates apoptosis of host cells and producing IL-1β. What is more interesting, according to *Arimatsu et al.,* research, oral administration of *P. gingivalis* induces changes in the intestinal microflora in the mouse model, increasing systemic inflammation. According to the research, *P. gingivalis* correlates with gastrointestinal tract malignancies, *A. actinomycetemcomitans* with pancreatic cancer and F. nucleate with cancer of the large intestine. Another mechanism of cancer formation as a result of periodontitis involves increasing the concentration of inflammatory markers, thereby releasing reactive oxygen that is able to initiate carcinogenesis (61,62,63).

A study conducted by *Michaud et al.,* shows the relationship between periodontal disease and cancer (also in people who have never smoked), indicating a significant association with lung cancer. In addition, the effect of oral hygiene correlates with the occurrence of cancer in the area of the head and neck, which is what the collective study of The International Head and Neck Cancer Epidemiology Consortium (64,65). It was found that patients with periodontitis are more exposed to have proximal colorectal neoplasms (CRN) and for advanced CRNs than people without periodontitis, but it is not an independent risk factor for general CRN and advanced CRN (61).

8. Ophthalmological complications

Odontogenic infections can spread through the continuity of tissues, mainly through the maxillary sinus, and reach the orbital fissure and orbit. That can cause orbital cellulitis or even abscesses, which may lead to impairment of the eye organs. Infections in the mouth can also potentially affect the development of diseases related to the organ's eyesight, for example, glaucoma (66,67).

8a. Glaucoma

Glaucoma is a neurodegenerative disease that causes irreversible damage to the optic nerve axes and retinal ganglion cells, resulting in worsening or loss of vision. One of the main risk factors for this disease is elevated intraocular pressure, however, periodontal inflammation may potentially contribute to the development of glaucoma by neurodegeneration of the nerves. The potential mechanism responsible for this pathology is the activation of microglia in the retina and optic nerve. Also as the reason is considered a shift in gene expression of the signal pathway and the complement of Toll-like receptor 4 (TLR4) (67,68,69).

Astafurov et al., conducted a study to determine if oral bacteria have been associated with the pathophysiology of glaucoma. It was found that patients with glaucoma had a larger

amount of bacteria Gram positive and Gram negative commensal bacteria, in saliva samples, in comparison to healthy people - what indicated on hypothetical correlation of increased amount of pathogenic bacteria in the saliva and neurodegenerative process. To determine the potential pathogenic mechanism, a research on animal models was performed. Among mices diagnosed with glaucoma, was observed increased activation of microglia in the retina and optic nerve was observed. That led to the disappearance of individual bundles of nerve fibers, resulting in fields defect (70,71).

8b. Abscess and orbicullar cellulitis

Rare complications of dental infections include ocular complications such as orbicular cellulitis or ophthalmia .Developing orbicular cellulitis may lead to abscess (72). Oral connective tissue inflammation is relatively rare and represents only 2% -5% of all cases of bacterial skin infections (73). However, it can lead to blindness due to rapidly progressing tension orbit - a clinical condition in which a hernia appears and causing the optic nerve destruction as a result of critical stretching. The consequence is impairment in the vision. Therefore, it is important that even the simplest dental cases require precision and awareness (74).

DeCroos et al., described a case report of a 40 years-old male with doubled vision, swelling around the right eye, facial pain and fever. The patient reported toothache on the right side of the maxilla, which occurred 3 days earlier. Imaging examination revealed periapical lucency, inflammatory changes in the maxilla and fracture of the maxillary sinus wall - which suggests that the root teeth infection was the cause of the patient's condition. Also, changes in the eye area, which confirm orbital cellulitis, was observed. One of the stages of patient treatment was the extraction of second and third molar teeth (75).

An orbital abscess with dental origin is a unique condition. In laboratory tests of pus swabs, occurs beta hemolyzing streptococci and *S. aureus* (76).

Arora et al., presented a case report of a 22-year-old female who reported with swelling of the right eye, which lasted for 10 days. The patient stated severe pain and swelling of the face, after removing the tooth, 3 weeks earlier. Swelling decreased as a result of conservative treatment - antibiotic therapy, however, remained visible after the end of treatment. In the physical examination, correct vision and limited mobility of the right eye along the lateral edge were found. The computed tomography and magnetic resonance revealed a thick-walled abscess on the right orbit, which overlapped the right lateral muscle of the eye. To protect the eye, the patient needed drainage of the abscess under general anesthesia (77).

CONCLUSIONS

Relations between commensal and pathogenic bacteria in the oral cavity are very sensitive for any changes. Imbalance in the oral cavity’s microbiome may result in the appearance of pathogenic lesions and directly or indirectly affect the health condition of the whole organism. Because of serious complications associated with oral health disorders, prevention and education in this area are so important.

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