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How does the periapical inflammatory process compromise general health?

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Several lines of evidence support the causative role of oral inflammatory lesions and certain systemic diseases, such as atherosclerosis and cardiovascular diseases, adverse pregnancy outcome and lung diseases. Properly executed epidemiologic studies identified increased odds ratios. Local or metastatic spread of oral microorganisms, local production of microbial or host-derived soluble regulatory molecules, that may initiate or sustain inflammatory events in remote tissues and organs and the presence of (a) common – extrinsic- or intrinsic-pathological mechanism(s) may result in or contribute to both local and systemic inflammation. A number of cross-sectional studies addressing a possible association between oral health and systemic diseases have also investigated the presence or the absence of periapical lesions. However, these studies cannot either confirm or refute a role of the periapical inflammatory lesion in the observed associations, since other variables of oral health might have exerted an inestimable influence on general health of the assessed population. The literature, dealing with patients with root canal infections and apical periodontitis as sole oral inflammatory lesions is extremely sparse. Our group has demonstrated that young adults with apical periodontitis exhibit certain biochemical changes, such as elevated levels of C-reactive protein and an increased whole blood chemiluminescence, which have been shown to elevate the risk for cardiovascular diseases. Future research will be required to determine whether and to what extent may endodontic diseases affect general health.

Apical periodontitis represents a periapical inflammation in response to long-standing, mostly microbial irritation from the root canal (1). Most research groups investigating chronic apical periodontitis focused on local immune-inflammatory reactions preventing the host from excessive microbial invasion on the one hand and resulting in tissue damage on the other hand (2, 3). The question whether direct cell-to-cell interactions – between bacteria and host cells as well as between different human cells – or autocrine and paracrine loops of stimulations may influence the function of remote tissues and organs resulting in the pathogenesis or contributing to the pathomechanism of systemic diseases was raised only by a few investigators (4). This article is aimed at summarizing briefly our current knowledge about associations between oral health and systemic diseases, understanding the possible pathomechanism and discussing observations made in chronic apical periodontitis patients.

Associations between oral health and systemic diseases

The undiscriminating practice of tooth extraction in the early 20th century as well as the 'quantum leap' experienced both by medicine and dentistry since that period of time, have virtually discredited the classic 'focal infection' theory, i.e. the concept of systemic inflammatory complications, that may arise from a localized oral, mainly dental infection, termed dental 'focus' (5). Recent epidemiologic studies however, have clearly indicated an association between impaired oral health, mainly because of periodontal diseases, and

an increased incidence of several important systemic diseases, such as atherogenesis, atherothrombosis and cardiovascular diseases, adverse pregnancy outcome, lung diseases, diabetes and osteoporosis (Fig. 1) (6). Although it is possible that the associations observed between oral inflammation and systemic diseases are coincidental, increasing body of evidence suggest a causal relationship in certain cases. Careful planning and evaluation of proper studies, as discussed by the paper of Caplan elsewhere in this volume, may help us to define the causal factors, acting singly or in conjunction with each other, that are directly and actively involved in the disease process and to differentiate them from risk indicators and associations explained by confounding factors (7).

Atherosclerosis and cardiovascular diseases

The most disturbing association linked oral inflammatory processes with atherogenesis and atherothrombosis that may progress to overt cardiovascular diseases, leading causes of human morbidity and mortality according to World Health Organization statistics (8). The recent definition of atherosclerosis as an inflammatory disease and the presence of overlapping risk factors, such as advanced age, male sex, distressed lifestyle, poor socio-economic status, diet and smoking suggested that a common pathway may exist in the pathogenesis and pathomechanism of certain oral inflammatory lesions, in particular marginal periodontitis and of atherosclerotic cardiovascular diseases (9, 10). Excellent reviews summarized the results of properly executed case-control and prospective studies that included thousands of individuals over many years and were conducted by different investigators from Europe and America concluding that there is an elevated risk of atherosclerosis and related cardiovascular diseases associated with oral inflammations (10–12). Conclusions however, should be carefully interpreted since neither the target population, nor the baseline dental measures, nor were the endpoints of these studies uniform. Most studies included more males than females. Different age groups were studied. Wide variety of descriptive measures, such as the number of missing teeth, total dental index, pantomography index, clinical attachment loss, extent of alveolar bone loss, various gingival and periodontal indices and the periodontal treatment need system were most

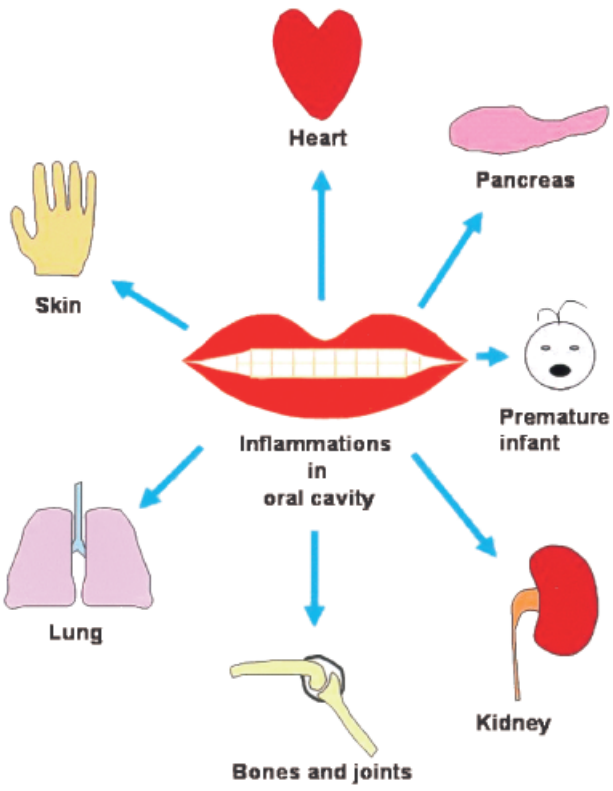

Fig. 1. Inflammation in oral cavity may impair the function of remote organs and tissues.

frequently used to characterize oral health condition. Fatal or non-fatal coronary heart disease, stroke, transient cerebral ischemia, a semiquantitative estimate of atherosclerotic mass and carotid intimal-medial thickness were considered as outcome measures (13–23). A need for critical interpretation of the results is stressed further by some studies having reached to a negative conclusion. A Finnish research group, investigating a large nation-wide sample of an adult population did not find a statistically significant association between oral health indicators and deaths related to coronary heart disease. Although the oral health status of the study population was determined by a thoroughly structured clinical examination performed by dentists, neither attachment loss nor radiological evidence of alveolar bone loss was assessed in the course of this study (23). Similarly, results from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study indicated that gingivitis was not associated, while periodontitis was associated with a non-significant increase in the risk for a coronary heart disease event (24). However, even after adjusting for known traditional epidemiologic, behavioral and biochemical confounding factors posing subjects at risk to develop cardiovascular diseases, the link between oral health status and cardiovascular diseases remained significant in the majority of studies indicating a causal association.

Adverse pregnancy outcome

Similarly, conflicting results have been published as to whether periodontal disease may contribute to preterm delivery or delivery of low birth weight (PDLBW) babies (6, 25). Interventional studies however, clearly indicated that periodontal therapy before 28 weeks of gestation significantly reduced the rate of PDLBW newborns in women with periodontal disease (26–28). The above reports not only indicate a casual relationship between periodontal disease and PDLBW in particular, but also underscore the importance of performing well-planned, randomized, interventional follow-up studies in investigating possible relations between oral health and systemic diseases.

Lung diseases

Recent evidences indicated a quite clear-cut association between periodontal and lung diseases as well (6). Bacteria causing aspiration pneumonia and ventilator-associated pneumonia have been demonstrated to originate from the subgingival dental plaque and the periodontal spaces in addition to the upper gastrointestinal tract (29, 30). Nosocomial pneumonia and bacteremia also has been shown to be significantly associated with dental plaque colonization in intensive care unit patients (31). The association between oral pathogens and initiation and exacerbations of chronic obstructive pulmonary disease is less obvious and requires further investigation (32).

The main pathways linking oral inflammatory lesions to systemic diseases

There are three basic mechanisms accounting for a possible association between oral inflammatory lesions and systemic diseases. (i) Local or metastatic spread of oral microorganisms. (ii) Local production of microbial or host-derived soluble regulatory molecules that may initiate or sustain inflammatory events in remote tissues and organs (Fig. 2). (iii) The presence of (a) common – extrinsic- or intrinsic-pathological mechanism(s) that may result in or contribute to both local and systemic inflammation.

Local spread of oral inflammatory lesions

Acute manifestations of oral bacterial inflammations, including periapical lesions may result in complications characterized by *per continuitatem* extension of the local infection towards adjacent tissues and organs. Purulent discharge may penetrate the oral mucous membranes and the skin resulting in sinus tract or fistula formation. The progression of bacterial infection may take a more generalized form involving the paranasal sinuses, the bones of the skull, the eye, the brain, the preformed soft tissue planes and spaces around the pharynx and the mediastinum. Severe, even life-threatening diseases, such as orofacial abscesses, cellulitis, deep cervical infections, mediastinitis, cavernous sinus thrombosis, acute osteomyelitis, requiring immediate surgical interventions and antibiotic therapy may develop (5, 33).

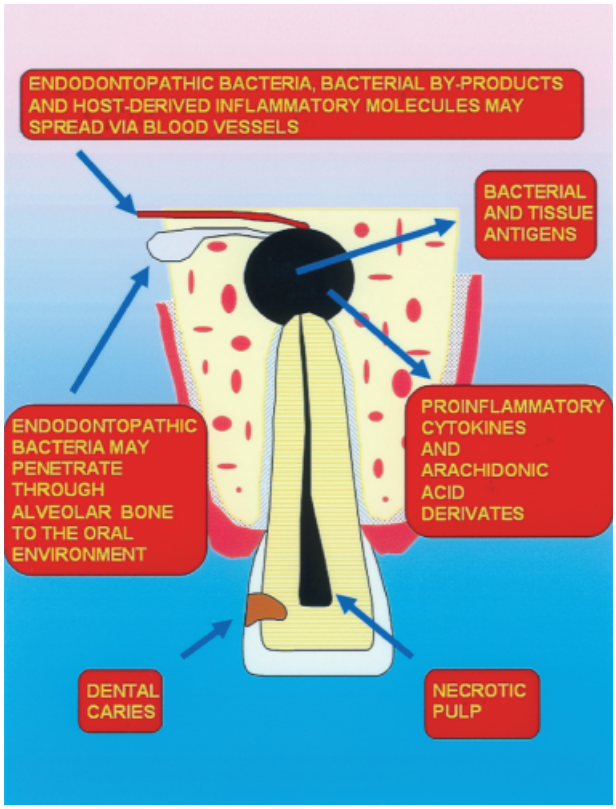

Fig. 2. The main pathways linking endodontic and periodontic inflammatory lesions to systemic diseases.

Metastatic infection I. Hematogenous spread of oral microbes to tissue surfaces of remote organs

The 'classic' example for 'dental focal infections' is represented by infective carditis when pathogenic bacteria eliciting endocardial infection originate from the oral cavity. Transient bacteremia is a well-known consequence of invasive professional dental treatments, including endodontic instrumentation approaching beyond the tooth apex and periapical surgery. The duration and the extent of bacteremia are related to the aggressivity and duration of the intervention, as well as to the number of bacteria inhabiting the area of the procedure. Other oral manipulations, including oral health procedures and common daily oral activities such as chewing and tooth brushing represent an even more frequent cause of transient, low-grade bacterial contamination of the bloodstream. The risk of bacterial invasion is particularly high in patients with periodontitis since a typical tooth with periodontitis is contaminated by 10^7–10^8 bacteria in the subgingival pocket and the size of the inflamed, exulcerated epithelial membrane may reach the volar surface of the forearm (5, 11, 34). Application of advanced microbiologic methods provided solid evidence for endodontic origin of bacteremia such as in patients following root canal treatment of teeth with apical periodontitis (35). However, colonization the endocardial layer and destruction of heart tissues, such as valves, by oral bacteria is a rare complication that occurs only in a selected group of patients at risk. Patients with a history of previous endocarditis, those with prosthetic cardiac valves and with certain congenital and acquired cardiac malformations require preventive antibiotic treatment in parallel with invasive dental interventions according to the guidelines of the American Heart Association (36). Similarly, immunocompromized patients, those on hemodialysis and those with total joint replacements may also develop metastatic infections originating form the oral cavity and, in selected cases, may benefit from prophylactic antibiotic therapy (5, 37, 38). Recent experimental evidence indicated that periodontopathic *Fusobacterium nucleatum* may infect the placenta inducing premature and term stillbirth in pregnant mice (39).

Metastatic infection II. Intracellular invasion

Repeated identification of *Chlamydia pneumoniae*, *Helicobacter pylori* and human Cytomegalovirus (CMV) in atheromatous lesions, as well as demonstration of elevated antibody titers to these microorganisms suggested that a direct infection of endothelial cells may be responsible for the genesis of atherosclerotic lesions in some patients (40). Recent demonstration of the ability of *Porphyromonas gingivalis* to invade aortic and heart endothelial cells shed a new light on the possible connection between the formation of atherosclerotic lesions and oral bacterial infections (41). DNA of periodontopathic/endodontopathic bacteria were repeatedly recovered from atherosclerotic lesions (42, 43).

Metastatic infection III. Airway inoculation by pathogenic bacteria originating from the oral cavity

Bacteria recovered from patients with aspiration pneumonia were shown either part of the indigenous oral microflora or nosocomially acquired pathogens (29). In the latter cases oropharyngeal colonization was a predominant factor of nosocomial pneumonia. DNA genomic analysis demonstrated that an identical microbial strain was isolated from oropharyngeal or gastric samples and bronchial samples of the majority of patients (44). An increasing ratio of positive dental plaque cultures for aerobic pathogens was observed in intensive care unit patients between days 0 and 10 of admittance. A high bacterial concordance was found between dental plaque and tracheal aspirate cultures (31). The results of the reviewed studies suggest that in critically ill patients competitive pressures favor the transcolonization of contagious structures of the oral cavity and the upper respiratory tract by endogenous pathogens, most frequently aerobic Gram-negative bacteria and *Staphylococcus aureus* resulting in the infection of the lower respiratory tract by these pathogens. The upper gastrointestinal tract, subgingival dental plaque and the periodontal spaces were suggested as likely sources of the transcolonizing microflora (30). In addition to the mechanical regurgitation and aspiration of the microbes, hydrolytic salivary enzymes may enhance the risk of inoculation and transcolonization of the pathogenic bacteria by unmasking mucosal surface receptors for bacterial adhesion molecules and by digesting sialic acid residues preventing of the formation of protective salivary pellicles (32). The amount and activity of these enzymes has been correlated with the periodontal and oral hygiene status of patients (45, 46).

Molecular mimicry I. Immunologic cross-reactivity

Another mechanism by which *C. pneumoniae*, the most often suspected infectious etiologic agent, has been connected with atherogenesis is molecular mimicry. The term is referred to the phenomenon of immunologic cross-reactivity between microorganisms and human tissues. Lymphocytes, originally sensitized by microbial antigens exhibiting sequence homologies with human antigens may develop auto-aggressive properties. T cell-mediated injury of cardiac myocytes in *Chlamydia* infections was proven initiated through antigenic mimicry between the bacterial 60 kDa cystein-rich outer membrane protein and M7Aα, the dominant autoaggressive epitope of the cardiac-specific α myosin heavy chain molecule (47).

Experimental observations suggested that a similar mechanism may explain for host tissue damage or an inflammatory type of response in remote organs induced by local oral infections. Highly immunogenic heat shock proteins (Hsp) of oral bacteria were demonstrated to share sequence homology with the human analogues (48). Because bacterial Hsp can mimic the effects of human Hsp immunogenic epitopes, the former molecules may activate host T-lymphocytes and result in an accumulation of auto-aggressive T-cells in a remote localization, e.g. in an early atheromatous lesion. The T-lymphocytes with overlapping anti-bacterial and anti-human Hsp specificities may contribute to the progression of the lesion in which human molecules were exposed to the sensitized T-cells by endothelial injury, initiated by factors independent from the oral bacterial infection having presented bacterial Hsp to immune recognition.

Vaccination against caries with *Streptococcus mutans* resulted in the production of cross-reactive antibodies with antihuman antivascular and anticardiac specificities (21).

Molecular mimicry II. Sequence homology of bacterial proteins with human regulatory molecules

A heptamer amino acid sequence of an outer membrane-associated protein of the oral pathogen *Strepto-*

coccus sanguis was shown to be identical to the platelet-interactive domain of Type I and III collagens equipping the microbe with a potential for inducing platelet aggregation, an event that has been shown to contribute to vascular plaque development (49). Platelets isolated from rabbits with hyperlipidemia, an established risk factor of atherosclerosis and related diseases, exhibited a particularly accelerated *in vitro* aggregation in response to *S. sanguis* (50). The two risk factors, i.e. *S. sanguis*-induced platelet aggregation and hyperlipidemia may thus mutually potentiate each other's effect. *P. gingivalis* was demonstrated to stimulate human platelet aggregation *in vitro* by a similar mechanism (51).

Bone marrow transplant children frequently develop a disseminated intravascular coagulation-shock-like syndrome because of *Streptococcus viridans* bacteremia (37). The majority of the isolated bacterium samples induced human platelet aggregation *in vitro* (50).

Soluble immune-inflammatory mediators may elicit systemic effects

Oral inflammatory lesions, elicited by pathogenic microorganisms, are connected with the expression, production and release of soluble regulatory compounds amplifying the consequences of local cell-to-cell interactions, as reviewed by Kiss elsewhere in this volume, and mediating inflammatory reactions to remote tissues and organs. Detection of biochemical markers of a chronic low-grade inflammation has repeatedly been reported in patients with cardiovascular diseases (52–54). Moreover, C-reactive protein (CRP), as a sensitive marker of inflammation has been indicated to predict future risk of cardiovascular diseases in initially healthy individuals (55, 56). Oral inflammatory lesions have been shown unequivocally to result in or, at least, to contribute to elevated systemic inflammatory responses (57–60). A recent study found elevated CRP levels in patients with atherosclerosis and in patients with periodontal disease. The most prominent increase in CRP concentration was observed in patients suffering from both conditions (61). These observations suggest that certain inflammatory mediators or other bioactive compounds induced by them represent possible intermediate factors that may link oral inflammatory lesions to atherogenesis, adverse pregnancy outcome, insulin-dependent diabetes mellitus and chronic obstructive lung disease (62–66).

Soluble mediators I. Microbial molecules

Among soluble factors, lipopolysaccharides (LPS), released from cell walls of Gram-negative bacteria are probably the most potent and best-studied components involved in systemic inflammatory response. LPS, present in the dental plaque and in the infected root canal can penetrate the gingiva and the periapical area in high concentration (67–69). LPS isolated from endodontopathic/periodontopathic bacteria have been shown to induce the production of an array of proinflammatory and chemotactic cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, interleukin (IL)-1α and -β, IL-6, -8, monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor (TNF)-α (70). It can activate neutrophil leukocytes and monocyte/macrophages, the complement system via the alternate pathway, the kinin cascade and the hemostatic system (71–74). The proinflammatory and procoagulant state, as well as the endothelial dysfunction elicited by LPS may contribute to atherogenesis.

In addition to LPS, there are a number of further cell components of oral bacteria that may contribute to the systemic inflammatory state by inducing inflammatory cytokines (70). CMV and Epstein–Barr virus (EBV) infections, which have recently been implicated in the development of root canal and periapical lesions, also can induce inflammatory and chemotactic cytokines (75). The deleterious effects of CMV and EBV on vascular endothelium elicited by influencing the cytokine network may become especially powerful in conjunction with LPS (76).

Soluble mediators II. Host compounds

As discussed above, one of the most important effects of bacterial molecules as well as herpesviruses is to induce the expression of human proinflammatory cytokines and chemokines. These are soluble glycoproteins with an extremely powerful regulatory potential virtually on every mammalian cells. Several pleiotropic and redundant effects cross the borders of target cell specificity. Both stimulatory and inhibitory autocrine/paracrine loops can modulate the effect of individual cytokines that may up- or downregulate their own specific receptors or that of other ligands modifying the response of the target cells. The combination of multiple interactions forms the cytokine network (77).

The cytokine profile of oral inflammatory lesions can stimulate production, recruitment and activity of each leukocyte subpopulation, including neutrophils, monocyte/macrophages and T-lymphocytes, which have been shown to play a pathogenic role in systemic diseases associated with oral diseases. TNF-α, IL-1 and macrophage (M)-CSF increase binding of low-density lipoprotein (LDL) to endothelium and smooth muscle and increase the expression of the LDL-receptor gene, thereby inducing endothelial dysfunction and smooth muscle cell proliferation (78). The same cytokines, together with IL-8 and MCP-1 upregulate cell adhesion molecules that attract activated leukocytes initiating and sustaining target organ damage (66). IL-1 is able to stimulate arachidonic acid metabolism to produce prostaglandin E_2 (PGE_2) and thromboxane A_2 with potent platelet aggregating and vaso/bronchoconstricting activities as well as leukotrienes, which can amplify the inflammatory response (9, 66).

The most studied chain of events is represented by the oral inflammatory lesion → (LPS) → IL-1/IL-6/TNFα → liver → positive acute phase proteins/coagulation factors → target organ axis. Positive acute phase proteins, including certain coagulation factors, such as fibrinogen, are synthesized by hepatocytes in response to IL-1, -6, and TNF-α (79). The University College London research group has recently published the results of a prospective, blind, interventional trial. These investigators observed an elevated serum IL-6 concentration in patients with severe periodontitis. IL-6 levels decreased significantly 6 months after delivering of standard, non-surgical periodontal therapy (80). Investigators from the Medical University of Warsaw found elevated IL-1 and TNF-α concentrations in response to acute coronary syndrome in patients with advanced periodontal disease (81). Some acute phase proteins, in addition to their inflammatory and risk-estimate marker function, as discussed earlier, may contribute to the injury of tissues remote from the oral inflammatory lesion. Fibrinogen, as a coagulation factor, obviously favors atherothrombotic events. Aggregated CRP may participate in the atherogenic accumulation of LDL that it binds selectively (82). Complexed CRP is able to activate the classic pathway of complement and can act proinflammatory (83). CRP induces the production of tissue factor that has clearly been related to coronary thrombotic events (84, 85). An Italian prospective study found a significantly higher probability of death in patients with periodontal disease and ischemic stroke who exhibited high CRP upon referral to the hospital or experienced a rise in the CRP level within the first 72 h when compared with those with persistently low or decreasing CRP concentrations suggesting that improved dental care and extensive use of anti-inflammatory drugs may decrease stroke mortality (63).

Common etiopathogenic factors may play a role both in oral and systemic inflammation

There are well-defined patient-related and environmental risk factors, such as age, smoking, diabetes, socio-economic status and lifestyle that are common in certain oral inflammatory diseases and systemic diseases. However, when considering the numerous biochemical factors that have been linked both to oral inflammatory lesions and to systemic diseases one may expect a more basic condition, playing a fundamental role both in local and systemic inflammatory events and connecting the biochemical markers to both of them and to each other. The research group from the University of North Carolina, as well as other investigators, has observed that some patients with early-onset periodontitis, refractory periodontitis and those with insulin-dependent diabetes mellitus have a hyperinflammatory monocyte phenotype. Peripheral blood monocytes, derived from such patients, produce 3- to 10-fold greater amounts of IL-1β, TNF-α, and PGE_2 than those obtained from normal individuals and patients with non-hyperinflammatory monocyte phenotype (18, 69). In mice, a hyporesponsive phenotype has been defined (86). These mice have been demonstrated to possess an impaired ability to respond to LPS because of a mutation in the gene that encodes Toll-like receptor 4 (TLR4) (87). In humans, polymorphisms, most often single nucleotide polymorphisms (SNP) of genes encoding for cytokines and enzymes influencing the function of immune cells have been shown to alter the intensity of immune reactions and may be responsible for the hypo/hyperresponsive pattern of monocytes and macrophages (80, 88, 89).

Are there evidences connecting periapical inflammatory lesions and systemic diseases?

A number of cross-sectional studies addressing a possible association between oral health and systemic

diseases have investigated the presence or the absence of periapical lesions. However, these studies cannot either confirm or refute a role of the periapical inflammatory lesion in the observed associations, since other variables of oral health might have exerted an inestimable influence on general health of the assessed population (13, 14, 90, 91). Investigating an association between acute cerebrovascular ischemia and chronic and recurrent infection in a case-control study, a research group from the University of Heidelberg has suggested that periapical lesions were more severe in the patient group than in the control group (19). A group from the Tokyo Dental College observed an association between immune responses to Hsp produced by oral bacteria, chronic marginal and periapical periodontitis, CMV infection, dental metal allergy, and their combinations (92).

The literature, dealing with patients with root canal infections and apical periodontitis as sole oral inflammatory lesions is extremely sparse. A group of investigators from the Oita Medical University reported on a case of a 45-year-old Japanese woman with chronic urticaria not responding to antihistamine therapy that became symptomless after having extracted decayed teeth and teeth with periapical abscesses and given root canal treatment to the other teeth with periapical radiolucencies (93). A recent cross-sectional Scandinavian study reported no statistically significant relationship between the number of apical periodontitis lesions and the presence of coronary heart disease in middle-aged-to-elderly women (94). Our group has investigated 36 young adults with apical periodontitis resulting in periapical radiolucencies of at least 3 mm in diameter. The patients were otherwise healthy. We have assessed serum and whole blood immune and inflammatory parameters on referral and following root canal treatment and apicectomy. We have measured the serum concentration of two strong acute phase proteins, CRP and α_2-macroglobulin (AMG), two moderate acute phase proteins, α_1-antitripsin (AAT) and haptoglobin (HPT) and 2-week acute phase proteins, complement component C3 and ceruloplasmin (CER). The levels of AMG and AAT fell significantly as early as 7 days after treatment. All investigated acute phase proteins decreased significantly 3 months after treatment (95). Pretreatment CRP level (mean $\pm$ SD: 6.6 ± 4.2 mg/L) was comparable with elevated CRP levels found in patients with periodontal disease and it was high enough to consider it as a cardiovascular risk factor as defined by the guidelines of the American Heart Association (57–64, 96). Similarly, we found an elevated whole blood chemiluminescence, which decreased significantly in parallel with the treatment, indicating an activated metabolic and functional state of the peripheral blood neutrophil granulocytes. No significant changes were noticed with respect of serum immunoglobulin concentrations and complement activity, and peripheral blood lymphocyte subpopulations (97). Local IL-1, -6 and GM-CSF production, as a cytokine source capable for inducing an acute phase reaction and systemic granulocyte activation was reported in human dental pulp and periapical lesions by our group as well as by others (98–101).

Conclusion

Several lines of evidence support the causative role of periodontal inflammatory lesion and certain systemic diseases. Properly executed epidemiologic studies identified increased odds ratios. The chronological sequence of events – i.e. oral inflammation precedes the development of systemic disease and anatomical differences – such as the finding that the majority of patients with coronary atherosclerosis do not exhibit severe atherosclerotic lesions in the region of the oral cavity (102) – argue strongly against an inverse relationship. Finally, there are some experimental models and, more importantly, a few interventional trials available that underscore the biological plausibility of the epidemiologic studies. In contrast to the periodontal diseases, a possible role for root canal infections and periapical lesions in eliciting a systemic disease cannot yet be decided. Future research will be required to determine whether and to what extent may endodontic diseases affect general health.

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