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The influence of chronic apical periodontitis on oral and general health

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In healthy condition, the periodontal space between the root surface and the alveolar bone is relatively poor in cells. In case of root canal infection however, large number of immune-inflammatory cells infiltrate the periapical region of the affected teeth. A major issue is if and to what extent microbial and host cells contribute to lesion formation and whether the local inflammation may impair general health. The question is important as it may fundamentally influence the therapeutic strategy in patients with apical periodontitis. The aim of this paper is to review the results of recent experimental and clinical observations that investigate the importance of cellular interactions in exerting protective and destructive effects in periapical inflammatory lesions. The majority of studies indicate that the lesion would not develop in the absence of permanent release of bacteria and their by-products from the infected root canal. On the other hand, the formation of the classical granulation tissue is dependent on the presence and proper function of host cells and regulatory molecules. The dynamic encounter of root canal microbiota and the local immune system prevents overwhelming bacterial infiltration of the periradicular space but it is also connected with degenerative changes, most importantly bone resorption, resulting ultimately in tooth loss. However, by the use of proper endodontic methods, the lesion can be successfully treated in the majority of cases. Remineralization of the lost hard tissue will occur or the lesion will transform into an inert periapical scar.

Key words: apical periodontitis, inflammation, microbiology, immunity

Introduction

Apical periodontitis is an inflammation of periapical tissues in response to irritative root canal stimuli. Although the initiating event is most commonly the infection of the root canal, lesion progression – and repair – is largely determined by local interactions of host cells. The periapical inflammatory infiltrate consists of the cellular and soluble components of the specific and nonspecific branches of the immune system [4, 22].

Depending on the intensity and duration of the pro-inflammatory stimuli, the periapical reaction may take either an acute or a chronic course. The histomorphology of the lesion correlates with the clinical stage of apical periodontitis [4]. Acute apical periodontitis is characterized by vasodilation, vascular congestion and edema. Neutrophil leukocytes and macrophages infiltrate the periapical ligament. The first line of host defense can effectively limit microbial invasion from the infected root canal. Virulent root canal microbes may establish a film on the external root surfaces or may form nests within the previously healthy periapex. In response, an abundant number of neutrophil leukocytes accumulate and the incipient acute lesion develops into primary periapical abscess [22]. Acute exacerbation of a pre-existing chronic lesion results in the development of a secondary abscess with similar morphology. In the incipient lesion, lamina dura disruption and bone resorption of the neighbouring spongiosa can be demonstrated by imaging approaches. Both primary and secondary abscess formation are accompanied by further significant loss of hard tissues giving space for the formation of a chronic lesion [42].

In chronic periapical lesions, which develop either as periapical granulomas or radicular cysts, exogenous irritative agents, usually root canal microbiota and their by-products, and host defense factors are in a dynamic equilibrium. In these cases, the immune mechanisms are not able to destroy and completely eliminate the pathogenic agents but, by forming a histologic as well as functional barrier, effectively prevent their further invasion [72]. The histological appearance of periapical granulomas represents every momentum of the periradicular inflammatory process from the acute incipient response to the burned-out end-stage lesion. Neighbouring histological structures, called necrotic, exudative, granulomatous and fibrous zones, penetrate into the surrounding alveolar bone in an onion leaf-like fashion starting from the apical foramen *(Fig. 1)*. According to the predominant zone(s), lesions can be classified as exudative, granulomatous, granulofibrotic and fibrotic granulomas [67, 105].

Over 50% of chronic periapical lesions contain epithelial strands originating from the epithelial rests of

Malassez [71, 92]. Coalescing epithelial strands form radicular cysts with a frequency varying from 6 to 55% of the lesions. The cavity of pocket or bay cyst communicates with the root canal. In contrast, the true cyst is independent of the root canal system. The epithelial lining of cysts is embedded into the inflammatory granulation tissue [22, 82, 84].

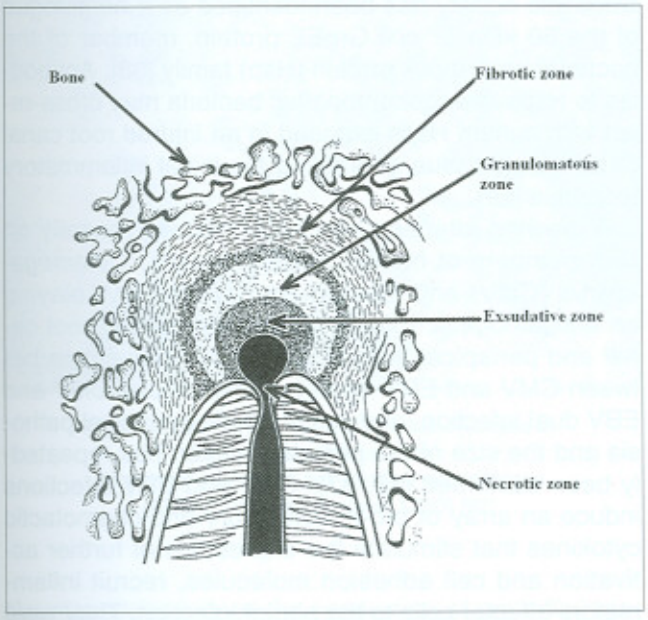

Figure 1.
Schematic structure of periapical granuloma

Apical periodontitis is a significant oral disease, as it may cause local symptoms, including pain and as it results in alveolar bone resorption and ultimately, tooth loss [72, 84]. The lesion has the potential to compromise general health, as well. Using contemporary non-surgical endodontic treatment, periapical lesions can be cured in about 85–90% of patients. Radiologic signs of recovery can be seen in 89% of cases after 1 year. However, complete disappearance of the lesion may take more than 2 years, indicating that active functioning of host repair mechanisms is as much important as the successful eradication of root canal infection. True cysts are characterized by a much higher endodontic treatment failure rate, therefore some investigators consider these lesions to be autonomous once initiated [14, 37, 74, 76].

In this article the delicate interplay of microbial as well as host cell interactions, which play a role in the initiation and in the development of different phases of the lesion including the healing process, will be reviewed. A brief overview will also be provided on the different mechanisms how apical periodontitis may impair general health of patients.

Microbial pathogenic factors in apical periodontitis

There is overwhelming evidence, including our own investigation, that the vast majority of the root canal of teeth with periapical lesions is infected [57]. Endodontopathic bacteria represent only a small minority of the over 500 species that colonize the healthy human mouth [98]. Early pulpal infections are characterized by aerobic and facultative anaerobic species. In parallel with local oxygen consumption, obligate anaerob bacteria become predominant [49].

A recent, carefully planned and executed histological study, investigating 50 human periapical lesions demonstrated, that bacteria were always present in the root canal of the affected teeth. Interestingly, in 18 of the 50 roots there was inflamed but vital pulp tissue in the apical part of the root canals [82]. This study has confirmed earlier investigations reporting that chronic periapical lesions were rarely contaminated except for actinomycotic infections. The presence of bacteria was repeatedly demonstrated only in the immediate vicinity of the apical foramen and in resorptive lacunae neighbouring the main apical foramen. Even in periapical abscesses and exudative-type of chronic lesions, bacteria only colonized in necrotic areas – surrounded by abundant, actively phagocytozing neutrophil leukocytes [45, 50, 73, 88].

Bacteria however, do not need to emigrate from the infected root canal to stimulate a periapical inflammatory response. There is a number of soluble bacterial products with a powerful pro-inflammatory potential. These compounds may attract phagocytes, representing the first line of defense, directly or by inducing the expression of pro-inflammatory cytokines and cell adhesion molecules by resident host cells. Other bacterial molecules can stimulate host regulatory molecules *(Table I)*. Lipopolysaccharides (LPS), present in and released from cell walls of Gram-negative bacteria are probably the best characterized components of endodontopathic bacteria to induce cytokines and other inflammatory compounds. LPS isolated from *A. actinomycetemcomitans, F. nucleatum, P. gingivalis* and *Prev. intermedia* have been shown to induce the production of an array of pro-inflammatory and chemotactic cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, interleukin (IL)-1α and -β, IL-6, IL-8, macrophage chemotactic peptide (MCP)-1 and tumor necrosis factor (TNF)-α [104]. Local IL-1, IL-6 and GM-CSF production was repeatedly detected in human dental pulp and periapical lesions [2, 47, 79, 102]. Interestingly, LPS preparations extracted from endodontopathic bacteria were shown to induce cytokine secretion in oral cells but not in skin-derived epithelial cells [19]. In contrast to most LPS preparations, *P. gingivalis*-derived LPS was shown to downregulate IL-8 and major histocompatibility complex (MHC) Class II antigenes in oral

epithelial cell lines. This immunosuppressive effect of *P. gingivalis* LPS may contribute to the successful bacterial invasion of periapical tissues [11, 19, 29].

There are other cell components of endodontopathic bacteria that are able to initiate inflammation [104]. Fimbrial protein extracts from *P. gingivalis* were demonstrated to increase the production of pro-inflammatory cytokines in stimulated host cells [20, 21]. A 12-mer amino acid sequence between residues 69 and 80, connected with the biological activities of the native fimbrial protein has been identified, opening a pathway for developing targeted therapy [75].

Table I.

Host regulatory factors induced by endodontopathogenic microorganisms

Cell adhesion molecules and ligands
ICAM-1
CD11/18
LFA-1
VLA-5, VLA-6
CD29, CD49
Chemokines and receptors
IL-8
KC
Macrophage inflammatory protein-1 and 2
Rantes
Pro-inflammatory cytokines, receptors and antagonists
GM-CSF
IL-1
IL-1R
IL-1Ra
IL-6
IFN-γ
TNF
Reactive oxygen and nitrogen intermediates and arachidonic acid metabolites
Superoxid anion
Hydrogenperoxid
Nitrogen-monoxid
Leukotrienes
Prostaglandines
Transcription factors
NF-κB
IE2-protein

The biological activity of surface-associated material (SAM) of certain Gram-negative bacteria may exceed that of corresponding LPS preparations. SAM prepared from *A. actinomycetemcomitans, E. corrodens* and *P. gingivalis* was shown to directly stimulate IL-6 synthesis of human gingival fibroblasts without affecting transcription of IL-1 and TNF genes that induce the expression of IL-6 by positive loops of stimulation upon challenge with LPS [80]. A 64 kDa protein component of *A. actinomycetemcomitans* SAM with potent osteolytic activity has been identified as a homologue of the 60 kDa *E. coli* GroEL protein, member of the bacterial heat shock protein (Hsp) family [38]. Antibodies to Hsps of endodontopathic bacteria may cross-react with human Hsps exposed in an injured root canal or periapical tissue, promoting the initial inflammatory response [89].

A growing attention has been focused recently on two members of human herpes viruses, *Cytomegalovirus* (CMV) and *Ebstein-Barr virus* (EBV) playing an etiopathogenic role in the development of root canal and periapical lesions. A positive correlation between CMV and EBV infection, in particular CMV and EBV dual infection, and symptomatic periapical pathosis and the size of the periapical lesion has repeatedly been confirmed [86, 87]. CMV and EBV infections induce an array of pro-inflammatory and chemotactic cytokines that stimulate the expression of further activation and cell adhesion molecules, recruit inflammatory effector cells to the site of infection. They were shown to dysregulate the receptor activator of nuclear factor-κB ligand (RANKL)/osteoprotegerin system, thereby contributing to alveolar bone resorption. These effects may become especially powerful in synergy with LPS [93, 107].

The role of host cells in the initiation and progression of the apical periodontitis lesion

Cells within the periodontal ligament surrounding the healthy root apex constitutively express cell adhesion molecules and chemokines in a low level providing a week stimulus for attracting and activating polymorphonuclear leukocytes and macrophages [28, 48]. This activity of innate immunity has been suggested to play a key role in maintaining clinically healthy periodontal and periapical tissues [11, 19]. In acute incipient apical periodontitis root canal bacteria reach the tooth apex resulting in the inflammation of the apical ligament and the neighbouring spongiosa accompanied by the well-known symptoms, such as pain, tenderness to percussion. Soluble microbial components upregulate the expression of first line pro-inflammatory cytokines, chemokines, cell adhesion molecules and low molecular weight inflammatory mediators, such as NO, inducing a robust influx of inflammatory cells into the periodontal ligament *(Fig. 2)* [17, 18, 62]. Subsequently, a second wave of inflammatory mediators, produced by the

stimulated resident and newly recruited cells, may amplify, propagate and prolong the expression of cell adhesion molecules and chemokine genes [66, 78].

In cases of noninfectious pulp necrosis, root canal and periapical inflammation can be elicited by sensory neuropeptides that are released from nociceptive nerve endings by a variety of noxious stimuli [5, 24].

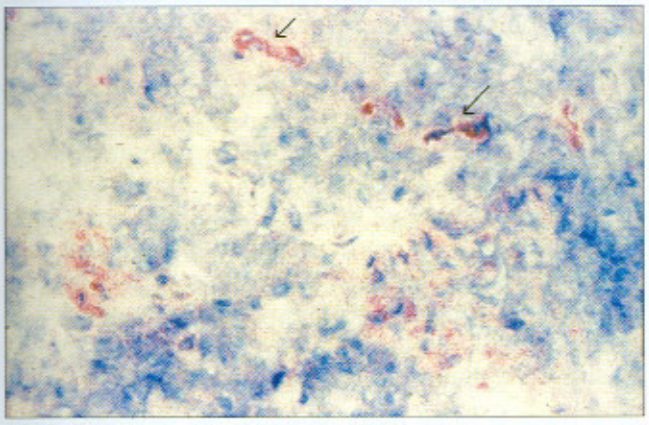

Figure 2. MCP-1 expression in endothelial cells of the granulomatous zone
Alkaline phosphatase anti-alkaline phosphatase (APAAP) labeling (arrows; X350) [62]

Neuropeptides induce the production of pro-inflammatory cytokines [51]. Both in human and experimental rattine periapical granuloma samples neuropeptide CGRP and substance P (SP) immunoreactivity was confined to nerve fibers in close proximity to blood vessels and inflammatory cells, including antigen-presenting cells (APC) and mast cells [32, 106].

The initial interaction between root canal microbes and resident host cells mount a robust and rapid protective response reaction by recruiting a large number of phagocytic cells, monocyte/macrophages and neutrophil leukocytes, to the sites of bacterial invasion, mainly to the immediate vicinity of the apical foramen [4, 82]. A variety of partially overlapping signals is involved in this process therefore, the exact contribution of individual cytokines and cell-to-cell interactions has yet to be determined [39, 42]. The attraction of infiltrating leukocytes requires them to transiently attach to endothelial cells, migrate through them and then to interact with cells and substrates in the extravascular tissue. This cascade is regulated by a set of cell adhesion molecules and the receptors for them, whereas the chemotactic signal can be provided by complement components of the alternative pathway of complement activation and by chemokines [7, 53, 69]. Expression of chemokines IL-8, MCP-1 and RANTES as well as vascular endothelial growth factor (VGEF)/vascular permeability factor (VPF) was detected in epithelial cells and in inflammatory cells in chronic periapical lesions [46, 62]. Pleiotropic (IL-1, TNF, stem cell factor), lineage-restricted (GM-CSF) and lineage-specific (granulocyte colony-stimulating factor, G-CSF and monocyte colony-stimulating factor, M-CSF) factors activate these infiltrating leukocytes to stimulate their effector functions [40, 41].

Neutrophil leukocytes, that are virtually absent in the healthy periodontal ligament, reach from the bone marrow via the circulating blood the infected root canal and inflamed periapical tissues. After exerting their protective role by phagocytosing invading bacteria, most neutrophil leukocytes die in human periapical lesions, indicating their short-lived effector cell nature [82, 101]. Newly recruited macrophages outnumber resident ones as demonstrated by immunohistochemistry, in situ hybridization and ultrastructural analysis. Actively phagocytozing macrophages of infiltrating phenotype and neutrophil leukocytes accumulate in great numbers just beneath the periapical abscess and always infiltrate epithelial strands, i.e. they are associated with bacterial and host cells that express chemoattractant molecules [33, 82]. Inhibition of leukocyte recruitment or activation either by disrupting regulatory signals mediated by IL-1, TNF, IL-6 and their receptors or by depressing bone marrow function resulted in a more widespread local bacterial infiltration, even in generalized infections [9, 30, 78].

If phagocytes fail to eliminate completely the invading microorganisms and the irritative effects of soluble bacterial by-products and viruses persist, the lesion becomes chronic and a characteristic, complex granulation tissue will be established as a protective host response to limit periapical tissue damage by localizing root canal microbiota and mitigating the inflammatory response. The initiation and formation of granulomas is largely dependent on the interaction of antigen-presenting cells with $CD4^+$ T-lymphocytes [91, 96]. Antigen-presenting cells activate $CD4^+$ T-lymphocytes through their antigen-specific receptors (TCR) in conjunction with MHC Class II molecules [81].

The sequence of events in periapical granuloma formation has been best studied in experimentally induced lesions in the rat [33]. In early lesions, established after 28 days of unsealed pulp exposure, MHC Class II-negative, actively phagocytozing macrophages accumulated in the vicinity of periapical abscess. In contrast, MHC Class II-positive macrophages were found evenly interspersed among other cell types within the cell-rich granulomatous zone. MHC Class II-positive dendritic cells (DC) were also noticed in great numbers, mostly located in the outer, fibrotic border of the lesion. Both MHC Class II-positive macrophages and DC established cell-to-cell contacts with MHC Class II-negative lymphocytes. These results indicate that local antigen presentation takes place in periapical lesions with DC being able to activate both naive and memory T-cells during primary and secondary immune responses, respectively and MHC Class II-positive macrophages, eliciting a secondary immune response [33]. A similar distribution and morphology of

macrophage and APC subpopulations were noticed in human periapical lesions by immunohistochemistry and flow cytometry *(Fig. 3)* [52, 58, 83].

According to their cytokine expression pattern, $CD4^+$ T-cells can be classified as T-helper 1 (Th1) cells that produce and secrete IL-2 and IFN-γ and Th2 cells that produce and secrete IL-4, IL-5, IL-6, IL-10 and IL-13.

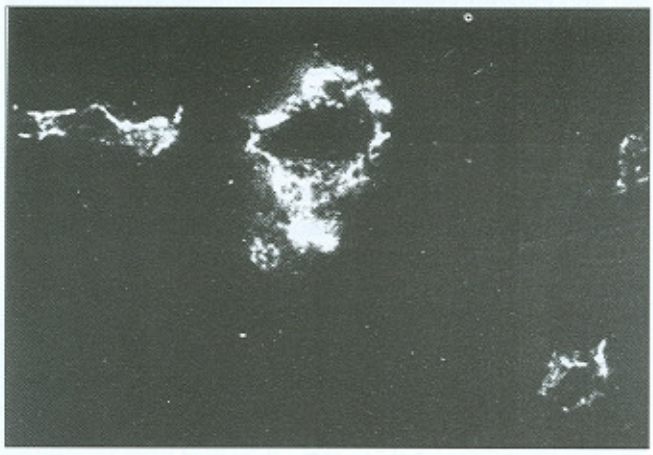

Figure 3
Surface membrane CD14 positivity of macrophages in periapical granuloma sample
Direct immunofluorescence reaction (anti-Leu M3-FITC monoclonal antibody; Becton-Dickinson, San Jose, CA, USA; X400)

Positive loops of stimulations exist between macrophages and Th1 cells as well as within the Th1 and Th2 subpopulations, respectively. In contrast, Th1 and Th2 cells exert a mutually inhibitory effect on each other. Th1-type cytokines augment cytotoxic T-cell functions, stimulate the expression of pro-inflammatory and bone resorptive molecules in other cell types, whereas Th2-type cytokines participate in B-lymphocyte stimulation to mount a humoral immune response and in dampening the inflammatory reactions [68]. Th1-lymphocytes prevail in early, expanding periapical lesions [31, 35]. As a result of positive loops of stimulation, the number of Th1 cells increases rapidly within the lesion.

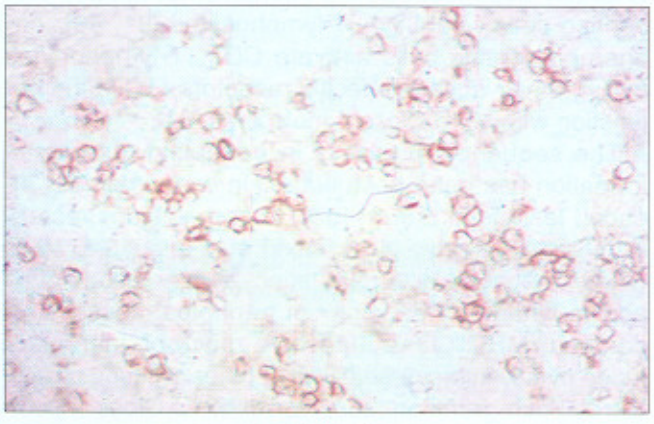

Figure 4
Cell surface (ringed) expression of CD25 antigen (IL2 receptor α) on activated T-lymphocytes in the granulomatous zone
Avidin-biotin-peroxidase complex (ABC) method (X250) [58]

In expanding periapical lesions, T-lymphocytes express activation markers, such as interleukin-2 receptor α-chain (CD25) and MHC Class II molecules, suggesting their active participation in anti-infective and pro-inflammatory reactions *(Fig. 4)* [58, 99]. This hypothesis was confirmed by demonstrating that immunosuppressive treatment resulted in a decrease in lesion size accompanied by a significant reduction in the number of CD25-positive cells in rat molars exposed to the oral environment when compared with non-treated controls [34]. In more advanced lesions Th2 cells slowly outnumber Th1 lymphocytes. The resulting change in the cytokine milieu is accompanied by a steady increase in the number of B-lymphocytes and plasma cells present in the lesion [52, 56, 102].

Cellular interactions resulting in periapical tissue damage

The immune-inflammatory cells of apical periodontitis possess a Janus-faced character. Anti-infective effector mechanisms are not limited to eradicate pathogenic microbes, "innocent bystander" host tissue components also fall victim. The most significant tissue injury involves the resorption of apical dentine and cementum, the mineralized matrix of the neighbouring spongiosa resulting in the loss of supportive alveolar structures and, ultimately, the affected tooth itself. The rate of bone loss is most expressed during the acute exudative phase(s), but it starts as early as in incipient apical periostitis and the osteolytic lesion keeps growing in association with granuloma formation and cyst development.

In course of bone remodeling, bone formation and resorption occur in parellel. The net result of this dynamic process is largely determined by the interaction of osteoblasts and osteoclasts. These two cell types communicate by the surface membrane-bound receptor–ligand pair, receptor activator of NF-κB (RANK) and its ligand RANKL, members of the TNF receptor and ligand families [97]. Osteoblasts express RANKL that binds to RANK present on the surface of osteoclast precursor cells. As a result of RANKL-RANK binding, osteoclast precursors differentiate into mature osteoclasts that become activated and resorb bone. Osteoblasts also express and secrete osteoprotegerin (OPG), the decoy receptor for RANKL, which inhibits RANKL-RANK interaction and thus bone resorption. Reciprocal gene expression of RANKL and OPG has been shown to play a key role in the coupling of osteoblast-osteoclast interaction [70]. Humoral regulatory molecules of bone resorption and formation, such

as hormones and cytokines exert their effects largely by influencing RANKL-RANK interaction directly or by changing the ratio of RANKL/OPG reciprocal gene expression [15]. Prostaglandins appear to act even more indirectly as permissive cofactors of bone-resorptive cytokines [44, 95].

Results from the extensively studied rat periapical granuloma model indicated that both positive and negative regulators of bone resorption were induced at the same time, rapidly after pulp exposure to the oral microflora. Peek levels of RANKL and pro-inflammatory cytokines TNFα, IL-1α and IL-1β preceded that of negative feed-back molecules OPG and IL-10. Therefore, early lesion was associated with alveolar bone loss and lesion expansion whereas severe progress of bone destruction was controlled in later phases of experimental apical periodontitis [36]. RANKL expression and local synthesis of bone-resorptive cytokines and arachidonic acid derivatives have been repeatedly described in human periapical lesions [10, 65, 85, 93, 103]. Bacterial compounds, such as LPS exert their bone resorptive effects rather indirectly, by inducing human molecules stimulating demineralization, then by direct bone destruction [61].

Impact of periapical inflammation on general health

Recent epidemiologic studies clearly indicated a causal association between impaired oral health and an increased incidence and severity of several important systemic diseases, such as atherogenesis, atherothrombosis and cardiovascular diseases, adverse pregnancy outcome, lung diseases, diabetes and osteoporosis [90]. The impact of apical periodontitis on general health is difficult to evaluate. In the majority of cases, there are several co-existing oral conditions and risk factors that may contribute to the untoward remote effect(s) of periapical inflammation. There are only anecdotal case reports on patients with root canal infections and apical periodontitis as sole oral inflammatory conditions. A group of investigators from the Oita Medical University observed a 45-year-old Japanese woman with chronic urticaria not responding to antihistamine therapy but she became symptom free after having extracted decayed teeth and teeth with periapical abscesses and given root canal treatment to the other teeth with periapical radiolucencies [94].

The "classic" example for "dental focal infections" is represented by infective endocarditis, where pathogenic bacteria originate from the oral cavity. Application of advanced microbiologic methods provided solid evidence for endodontic origin of bacteremia in patients following root canal treatment of teeth with apical periodontitis [12]. Recent demonstration of the ability of *Porphyromonas gingivalis* to invade endothelial cells shed a new light on the possible connection between the formation of atherosclerotic lesions and oral bacterial infections [13]. DNA of periodontopathic/endodontopathic bacteria were recovered from atherosclerotic lesions [23].

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, the evidence of these investigations was not conclusive enough to establish or to discard a clear role of the periapical inflammatory lesion in deteriorating general health [54, 63, 64, 100]. 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 [16]. 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 [43].

In the early 1990s, our research group have performed an interventional follow-up study involving 36, otherwise healthy young adults with apical periodontitis. We have assessed serum and whole blood immune and inflammatory parameters on referral and following root canal treatment and apicoectomy. We have measured the serum concentration of two strong acute phase proteins, C-reactive protein (CRP) and α_2-macroglobulin, two moderate acute phase proteins, α_1-antitripsin and haptoglobin and two week acute phase proteins, complement component C3 and ceruloplasmin. The levels of the investigated acute phase proteins decreased significantly after treatment [55]. Pretreatment CRP level (mean±SD: 6.6±4.2 mg/L) was high enough to consider it as a cardiovascular risk factor as defined by the guidelines of the American Heart Association [77]. 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 in patients with chronic apical periodontitis [60].

A novel, interesting way of possible association between periapical inflammation and general health is represented by polymorphisms of genes encoding for cytokines and enzymes influencing the function of immune-inflammatory cells. In the presence of certain polymorhic alleles both local and general inflammatory responses can be more intensive and the accompanying complications more severe than in the absence of the given allele [1, 8]. Peripheral blood monocytes of "hyperinflammatory type" patients with periodontal disease produce 3- to 10-fold greater amounts of IL-1β and TNF-α than those obtained from normal individuals [3, 25]. In murine monocytes, an impaired ability to respond to LPS from endodontopathic bacteria has

been attributed to a mutation in the gene that encodes toll-like receptor 4 [6, 27].

Healing of the periapical lesion

The development of acute incipient apical periodontitis is a consequence of the persistent root canal infection. However, most periapical lesions very rarely heal spontaneously and are not self-limited despite the powerful local protective immune-inflammatory reactions. Effective disinfection of the root canal system combined with proper root canal treatment is essential for the healing of the periapical lesion. After successful elimination of the initiating root canal infection by proper endodontic and restorative treatment, repair mechanisms of the granulation tissue may prevail over tissue destructive events. In contrast to early, expanding periapical granulomas, $CD8^+$ cytotoxic/suppressor T-lymphocytes usually outnumber $CD4^+$ helper/inducer T-cells in advanced lesions contributing either to a more effective elimination of infected and destructed cells or to the suppression of the intensity of inflammatory reactions, or both [59, 96]. In parallel with this process, the Th1 nature of the early periapical inflammation changes to Th2-type lesion. Th2 lymphocytes stimulate B lymphocyte production and immunoglobulin synthesis, which also may contribute to the eradication of residual periradicular infection *(Fig. 5)*. The functional significance of local humoral immunity in limiting advanced periapical lesions is emphasized by the observation that B-cell-deficient mice – but not T-cell- or complement-deficient mice – were at risk to develop disseminated anaerobic infections following experimental root canal infection [26].

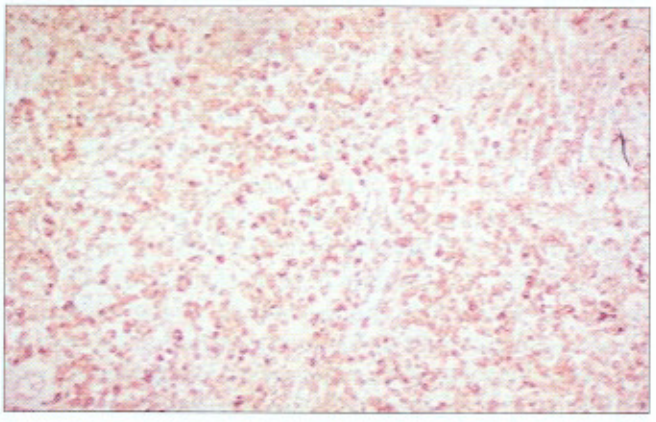

Figure 5
Abundant number of B-lymphocytes and plasma cells in the granulomatous zone of periapical granuloma
Immunohistochemical reaction (ABC method) using mixed polyclonal anti-heavy chain (anti-IgA+IgG+IgM) antibody (X160) [56]

With the exception of true radicular cysts, the proportion of which is not exactly characterized, the majority of periapical lesions improve significantly by conventional endodontics [37, 76]. The lesion may heal either completely by remineralization, as indicated by the disappearance of the former radiolucent area, or it may develop into fibrotic periapical granuloma, an inert periapical scar tissue.

Concluding remarks

Recent advances in the understanding of the network of interactions of endodontopathic microbes, immune-inflammatory cells of the host and their soluble products have changed our concept on apical periodontitis. Periapical inflammation develops usually in response to root canal infection. A cascade of bacterial irritation, induction of pro-inflammatory cytokine production and ceil adhesion molecule expression by a few resident cells of the narrow periradicular space recruit an extensive number of immune-inflammatory cells which form the highly organized structures of chronic periapical lesions. The granulation tissue exerts a protective function on the one hand by preventing the invasion of the periapical area by root canal microbes. However, it is the same granulation tissue that causes degenerative changes, most importantly the resorption of hard tissues. Extensive local inflammation may impair general health, as well. This chain of events, leading ultimately to the loss of the affected tooth, can be disrupted by disinfection of the root canal using proper endodontic treatment. Surgical intervention, such as apicoectomy and periapical curettage is necessary only in selected cases, since the granulation tissue has the capacity of healing, once constant irritation from the root canal has been eliminated. This dynamic equilibrium of protective function, degenerative and regenerative changes is regulated by the presence and proper function of host cells and regulatory molecules. Inhibiting leukocyte recruitment or activation result in a widespread local bacterial infiltration, even in generalized infections. Neither can remineralization of the lost hard tissue occur without the active functioning of the granulation tissue. Recent advances in the understanding of the pathomechanism of the periapical inflammatory processes resulted in a change in the treatment strategy of this disease. This paper may provide the practicing dentists a theoretical background to choose the proper treatment for their patients.

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