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RESEARCH ARTICLE

IMMUNE MODULATION IN PERIAPICAL INFLAMMATION OF ENDODONTICALLY TREATED TEETH

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ABSTRACT

Periapical inflammation occurs as a consequence of insult to the dental pulp in different ways including infection, physical and iatrogenic trauma, and, following endodontic therapy by the damaging effects of root canal filling materials. A problem of endodontic origin is solved mainly by cleaning and disinfecting the root canal system that in turn is dependent on various factors which includes efficient instrumentation, type of irrigant used and the technique applied for irrigation, intracanal dressing, the apical limit of the root canal preparation and obturation, and last but not the least, the quality of the sealer. Moreover, the use of systemic medicines is a great auxiliary in combating pain, inflammation and infection, thus helping to alleviate the clinical symptoms and accelerate the process of healing. The systemic therapy is indicated for treatment of an inflamed and infected pulp can assist in tissue repair by the modulation of the host's immune response. Nevertheless, different therapeutic factors and clinical conditions may interfere in this process of periapical healing. Hence, it is of fundamental importance that the dentist knows about the type of medication to be used in each case and whether systemic therapy is really necessary in a particular case through a comprehensive case evaluation. Hence, this review aims to discuss the success of root canal treatment by presenting the clinical indications of systemic medication application in endodontics. This will aid the professional in achieving more effective results with respect to periapical inflammation.

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INTRODUCTION

Periapical disease, an inflammatory disease mainly caused by dental caries, is one of the most prevalent infectious diseases of humans, affecting both children and adults. The infection travels through the root, leading to inflammation, bone destruction, and severe pain for the patient (Liang Hao) Dental pulp is protected from microorganisms of the oral cavity by enamel and dentin. The exposure of dental pulp to microorganisms and their products, as a consequence of dental caries, fractures, or operative procedures, triggers a local inflammatory response. The progression of such infection and inflammation results in necrosis of the pulp and consequent involvement of periapical tissues, generating a periapical lesion (Nair, 2000 and 2004). The periapical 'lesion' represents a local immune response to infection of the pulp and may be viewed, teleologically, as a second line of defense, the purpose of which is to localize the infection within the confines of the root canal system (Stashenko, 1990).

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A large body of evidence suggests that host-derived mediators which are induced by the infective process are critical in stimulating periapical inflammation and tissue destruction. These mediators play various roles in helping to combat infection, but may do so at the price of stimulating tissue damage (Stashenko, 1998). The direct effectors of periapical inflammation include cytokines, arachidonic acid metabolites, neuropeptides, and other endogenous mediators. Microbial infection is an absolute prerequisite for the emergence of apical periodontitis in a non-treated tooth (Vernal, 2006 and Leisinger, 1993). Necrotic tissue alone in the pulpal space is unable to sustain inflammatory lesions in the periapical tissue environment. For example, following an ischemic injury by trauma, total pulp necrosis may develop without bacterial involvement; apical periodontitis will not be established unless the pulpal space is infected (Vernal, 2006 and Leisinger, 1993). This may occur sooner or later as necrotic tissue, like anywhere in the body, serves as a growth medium ready for microbial colonization (Bergenholtz, 1975 and Richard, 2002). In periapical lesions, an initial short acute inflammatory response of varied intensity is accompanied by pain, tooth elevation, and tenderness to percussion. Tissue changes are

characterized by hyperemia and neutrophil recruitment, usually limited to the periodontal ligament. With the continuous presence of irritants at periapex, the acute response shifts to the formation of a granulomatous tissue with chronic inflammatory cells and fibrbroblasts: the apical granuloma (Nair, 1997 and 2004). These pathological changes in periapical tissues are the clinical consequence of the host defensive reaction against bacterial products that egress through apical foramen from infected dental pulp (Nair, 2000; Vernal, 2006 and Kawashima, 2007). This response is characterized by the persistent migration of polymorphonuclear leukocytes, monocytes, lymphocytes, plasma, and mast cells to the infected sites, and it largely prevents microbial invasion into the periapical tissues (Nair, 1997; Rodini, 2001; Liapatas, 2003). Periodontal disease is a chronic bacterial infection that affects the gingiva and bone that supports the teeth. The genetic and environmental factors seem to increase the susceptibility of some individuals in developing this severe inflammatory disease (Feng, 2006). It is also well recognized that the presence of only pathogenic bacteria is insufficient to cause periodontitis. Progression of this disease occurs due to a combination of factors, including the presence of periodontopathic bacteria, high levels of proinflammatory cytokines, matrix metalloproteinases (MMPs), prostaglandin E2 (PGE2), low levels of anti-inflammatory cytokines including interleukin-10 (IL-10), transforming growth factor (TGF-β) and tissue inhibitors of MMPs (TIMPs) (Gemmell, 2004). Inflammatory periodontitis lesions are caused by a group of periodontopathic bacteria and are characterized by large numbers of B cells and plasma cells together with a significant number of T cells and different concentrations of Th1 and Th2 cytokines (Fisman, 2008 and Seymour, 2000).

Periapical responses: Apical periodontitis is an inflammatory lesion in the periodontal tissues that is caused mostly by bacterial elements derived from the infected root canal system of teeth. In non-treated teeth apical periodontitis represents a defensive response to a primary infection in a necrotic pulp. Apical periodontitis may also develop due to a secondary infection subsequent to endodontic treatment procedures. Post-treatment apical periodontitis is most commonly due to either unsuccessful control of primary root canal infection by endodontic treatment measures, or infection or reinfection of the root canal system due to inadequate obturation and/or inadequate coronal seal that allowed bacterial leakage to take place. Inadvertent extrusion of certain medicaments and root filling materials into the periapical tissue compartment may also cause tissue toxic effects as well as precipitate foreign body reactions (Zvi Metzger).

Asymptomatic apical periodontitis: Asymptomatic Apical Periodontitis is inflammation and destruction of the apical periodontium that is of pulpal origin (https://www.aae.org/specialty/wpcontent/uploads/sites/2/2017/07/endodonticdiagnosisfall2013.pdf). Apical periodontitis serves an important protective function, aimed at confining bacteria discharged from the root canal space and preventing them from spreading into adjacent bone marrow spaces and other remote sites. The process is unique in the sense that it cannot eradicate the source of infection. The reason is that once a pulp has become necrotic, defense mechanisms cannot operate far into the root canal due to the lack of vascular support (Zvi Metzger). Bone loss that appears in radiographs serves as the main clinical indicator for the presence of apical periodontitis as many of these lesions are silent and prevail without overt clinical symptoms (Zvi Metzger). It appears as an apical radiolucency and does not present clinical symptoms (no pain on percussion or palpation) (https://www.aae.org/specialty/wpcontent/uploads/sites/2/2017/07/endodonticdiagnosisfall2013.pdf). Asymptomatic apical periodontitis is mostly biofilm derived (Schoeffel, 2008). Yet, acute forms do occur and may develop during the expanding phase of the initial lesion.

Symptomatic apical periodontitis: Symptomatic Apical Periodontitis represents inflammation, usually of the apical periodontium, producing clinical symptoms involving a painful response to biting and/or percussion or palpation (https://www.aae.org/specialty/wpcontent/uploads/sites/2/2017/07/endodonticdiagnosisfall2013.pdf). Symptomatic apical periodontitis results mostly from the action of planktonic bacteria (Matsumoto, 2008 and Schoeffel, 2008). Lesions of symptomatic apical periodontitis may also emerge as a result of a disturbed equilibrium between the host defense and the bacterial infection in an already established lesion.This may or may not be accompanied by radiographic changes that is depending upon the stage of the disease, there may be normal width of the periodontal ligament or there may be a periapical radiolucency. Severe pain to percussion and/or palpation is highly indicative of a degenerating pulp and root canal treatment is needed (https://www.aae.org/specialty/wpcontent/uploads/sites/2/2017/07/endodonticdiagnosisfall2013.pdf). It may develop as a direct consequence of the breakdown and infection of the pulp within a previously healthy periapical region (Zvi Metzger).

Immune response to periapical insult: Innate immunity has a considerable ability to recognize bacteria as non-self agents because these microorganisms present PAMPs in the bacterial wall, which are recognized by pattern recognition receptors (PRRs) on immune cell surfaces. PAMPs are invariant and represent conserved molecular patterns that are essential for microbial survival. They are found in bacterial lipopeptides, peptidioglycan, flagellin and DNA, with others that are specific either for Gram-negative (lipopolysaccharide (LPS)) or Grampositive (lipoteichoic acid) bacteria (Bascones-Martínez 2009 and Elson, 2007). Bacterial elimination in periapical lesions is carried out by PMNs. All other constituents and processes in apical periodontitis may be viewed as serving this ultimate goal. Local recruitment of PMNs from the capillaries, by ICAM-1–mediated margination, depends on interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα) derived from activated macrophages. Specific immunoglobulins are essential for effective phagocytosis. Their local production requires antigen presentation followed by activation of specific T-lymphocytes to produce a set of cytokines that will (i) allow proliferation of antigenspecific B-lymphocytes and their maturation into specific IgG-producing plasma cells and (ii) interferon gamma (INFγ) that activates macrophages to produce the IL-1 and TNFα required for the above tasks, as well as IL-8 which further activates the PMNs. All this elaborate network of cells and events serves one cause: bacterial elimination by PMNs [40]. Both T and B cells are present in periodontal disease tissues. The infiltrate in the periodontal lesion consists of lymphocytes, macrophages, neutrophils and mast cells that migrate to the tissue, guided by the different concentrations of chemokines and cytokines. INF-γ (Th1 response) produced by T cells would enhance the phagocytic activity of macrophages and neutrophils and contain the infection. However, if there is IL-4 production

(Th2 response), B cells are activated and start antibody production (Albandar, 2001).

Periapical lesion: Periapical lesions result from pulp necrosis induced by bacterial infection. The infection produces an inflammatory reaction first within the pulp and subsequently in the periapical region after egress of microorganisms, their by-products, and/or altered pulp tissues from the infected root canal. The periapical lesion is characterized by the presence of numerous inflammatory cells, which then lead to immune inflammation of periapical tissue. Generally, the body's immune defense system gradually removes the pathogens after the removal of bacterial infections, but during the process of obliterating foreign microorganisms, inflammatory factors produced by the body can also damage the surrounding normal tissue and cause periapical bone tissue absorption (Liang Hao) Periapical lesions are inflammatory conditions of tooth periapi Liang Hao cal tissues, triggered by dental pulp infection and characterized by exudation of immune cells to the affected tissues and production of inflammatory mediators such as cytokines. The inflammatory periapical reaction is mainly driven by Th1, Th2, and Th17 responses, and such polarization may modulate progression of the disease and expression of bone proresorptive cytokines (Celso Martins Queiroz-Junior, 2010).

Inflammation: These inflammatory responses are complex and consist of diverse elements. Immediate-type responses including vasodilatation, increased vascular permeability, and leukocyte extravasation-are mediated by endogenous mediators, including prostanoids, kinins, and neuropeptides. Non-specific immune responses including polymorphonuclear leukocyte and monocyte migration and activation, and cytokine production-are elicited in response to bacteria and their products. Acute inflammation (also known as innate immune response) is the first body response to injury. It is a protective body response against invading traumatic or microbial injury. The cardinal signs of inflammation include: hotness (calor), redness (rubor), swelling (tumor) and pain (dolor) (Sara Ibrahim, 2015), Immediately after microbial invasion, chemo attractants (e.g. endogenous chemical mediators) are released. Sources for these chemoattractants are various including; innate immune cells, platelets and microorganisms (Larjava, 2012). Chronic periapical inflammation further involves specific T- and B-cell-mediated anti-bacterial responses, and activates a network of regulatory cytokines which are produced by Th 1- and Th2-type T-lymphocytes (Stashenko, 1998). Anti-inflammatory cytokines (e.g.: interleukin4 "IL-4", interferon-alpha "IFN-α" and granulocyte-colony stimulating factor "G-CSF") also get released at the injury site. They try to counteract and regulate the effects of the pro-inflammatory cytokines and to drive tissues to the normal state (Opal, 2000). The balance between the pro- and antiinflammatory molecules determines the outcome of the inflammatory and healing processes. When the inflammatory process is resolved, tissue destruction is mild; consequently, regeneration occurs (replacement of the same type of dead cells). Persistent inflammation, however, leads to more tissue destruction as it is the case in marginal and apical periodontitis. Interleukin- and prostaglandins in particular have been implicated as central mediators of periapical bone resorption.

Bone resorption as a result of inflammation: Bone resorption is mediated by bone-resorptive cytokines produced by the inflammatory response. Consequently, the question of how to control an excessive inflammatory response in the inflammatory process while inhibiting corresponding bone resorption is particularly important (Liang Hao). Bone resorption is also stimulated by this inflammatory response, and space is created for the infiltration of immune cells, which are then organized into a barrier to sequester the infection. Bone resorption and bone formation are processes involving the activity of osteoclasts, osteoblasts, and osteocytes; they are affected by the systemic and local conditions (Seltzer, 1988). However, bone homeostasis is disrupted during apical periodontitis, which promotes increased rates of bone resorption (Roberto Holland, 2017). Boyle *et al*. (2003). suggested that the integrity of bone tissues depends on the maintenance of an equilibrium between bone resorption by osteoclasts and bone deposition by osteoblasts. The major regulatory mechanism of osteoclast activity seems to be performed by members of the TNF family of receptors, RANK (receptor activator of nuclear factor-β), osteoprotegerin (OPG), and the RANK ligand (RANKL). RANK is expressed on osteoclastic precursors and on mature osteoclasts, while RANKL, a transmembrane protein, is expressed particularly on osteoblasts under homeostatic conditions. Interactions between RANK and RANKL are required for the differentiation and activation of osteoclasts, an event regulated by OPG, which strongly inhibits bone resorption by preventing RANK-RANKL engagement (Boyle 2003). Interestingly, RANKL also induces the production of some substances, such as MCP-1/CCL2, which could contribute to bone resorption (Kim, 2006).

Resolution: Resolution process serves as an agonist to the inflammation phase, as the pro-resolution molecules act to reduce the infiltration of neutrophils to the injury site. They also promote the clearance of apoptotic cells and microbes by macrophages. In addition, they stimulate the antimicrobial activities of the epithelial cells (Nair, 1997 and Rodini, 2001). If the inflammation resolves, there will be minimal tissue destruction. However, in unresolved inflammatory conditions where elimination of the insulting molecules is not obtained, inflammation might continue. This will increase the production of the arachidonic acid derivative lipoxin A4 LXA4 (in response to pro-inflammatory mediators) that in turn function to minimize tissue damage and resolve the inflammation [30]. Regeneration involves a process of tissue renewal with cells that have similar characteristics to those that were previously lost; it is the morphological and functional restoration of tissue. Conversely, repair is characterized by the formation of connective tissue at the site of the lesion, and the infiltration of fibroblast. The process of healing begins with inflammation, and is resolved by the clearance of the immunogen that induces the tissue response (Childs, 2017). Complete repair only occurs once the antigen has been neutralized during the inflammatory response. During pulp infection, the occluded blood supply of the root canal becomes conducive to bacterial proliferation. Furthermore, inflammation within the periapical region is elicited to neutralize the antigen.

Regulation of immune response: OPG is a soluble secreted protein that lacks transmembrane and cytoplasmic domains. It binds to a receptor activator of nuclear factor-κB ligand (RANKL) whose receptor is the receptor activator of NF-κB (RANK), and inhibits RANKL/RANK signalling. The OPG/RANKL/RANK system in bone and vasculature is well known to work on bone metabolism and vascular calcification.

In addition, immune cells express these molecules, and this system is believed to be associated with the regulation of inflammatory and immune responses .RANKL is expressed in CD4+ T cells and macrophages, whereas OPG is expressed in mature B cells and macrophages. RANK is expressed in macrophage and dendritic cells. One of the functions of RANKL/RANK signalling in the immune system is to control the thymocyte-mediated medulla formation and the formation of self-tolerance in T cells, as well as the number of regulatory T cells (Treg). Additionally, RANKL directly contributes to the regulation of proinflammatory cytokine production in macrophages (Asagiri, 2008).

Resolvin: Resolvins (resolution phase interaction products) are a new group of bioactive lipid mediators produced naturally in the human body from ω3-polyunsaturated fatty acids (ω3-PUFA). They have a significant role in the resolution of inflammation (Serhan, 2005; Seki, 2009; Serhan, 2008; Tian, 2009; Weylandt, 2007 and Zhang, 2013). They are produced by oxygenation of ω3-PUFA derivatives, docohexapentaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA is theprecursor for D-series resolvins (RvD1, RvD2, RvD3 and RvD4) (Serhan 2005; Weylandt, 2012 and Serhan,) while EPA is the precursor for E-series resolvins (RvE1, RvE2 and RvE3) (Weylandt, 2012 and Isobe, 2012).

Function of resolvins: They appeared to cause a clear and dramatic anti-inflammatory effect on many diseases. Hasturk and co-workers in 2005 (Hasturk, 2006), showed the effects of Resolvin E1 (RvE1) on bone destruction in periodontitis. Their results showed that topical application of RvE1 significantly inhibited bone and tissue damage. In 2010, Elsharkawi *et al* (El-Sharkawy, 2010), systemic application of omega-3 PUFAs in a chronic periodontitis model. The results revealed a significant reduction in the severity of chronic periodontitis (i.e.: attachment gain and decreased probing depth) in patients who used supplementation of omega-3 PUFAs in combination with Aspirin when compared to the placebo group.

Effects of RvD1 on gene expression: The lower dose of RvD1 (10 ng/ml) induced statistically significant up-regulation of ALP when compared to control group. In contrast, the higher dose of RvD1 (100 ng/ml) induced downregulation of ALP in both presence and absence of TNF-α but it was not statistically significant (Sara Ibrahim, 2015).

Endodontic flare UP: Flare-ups can occur after root canal treatment and consist of acute exacerbations of an asymptomatic pulpal and/or periradicular pathologic condition. A flare-up represents a shift from or disruption of an established balance between bacteria and the host. Exacerbation is another term used, which implies worsening of a clinical condition from a silent, asymptomatic process to one presenting with overt clinical symptoms, i.e. pain, tenderness and swelling (Zvi Metzger). The causative factors of interappointment pain encompass mechanical, chemical, and/or microbial injury to the pulp or periradicular tissues. Microorganisms can participate in causation of interappointment pain in the following situations: apical extrusion of debris; incomplete instrumentation leading to changes in the endodontic microbiota or in environmental conditions; and secondary intraradicular infections (Sipavičiūtė, 2014). The symptoms associated with an endodontic flare-up are a function of oedema formation in the periapical area, resulting from local activation of the complement system. As bacterial antigens are introduced in the periapical tissue, specific immunoglobulins present against these bacteria will immediately engage the antigen and form immune complexes that activate the complement system (Zvi Metzger). The causative factors associated with interappointment flare-ups have been examined in many studies. These risk factors can be divided into two broad areas: the patient presenting factors, and what procedures were performed by the dentist. Interestingly, the literature clearly and consistently shows that some of the patient presenting factors are much more powerful than treatment procedures as related to the risk for developing a postendodontic flare-up (Richard, 2002). The post-treatment pain is neither prevented nor relieved by medicaments such as formocresol, camphorated paramonochlorophenol, eugenol, iodine potassium iodide, Ledermix, or calcium hydroxide. However, the use of intracanal steroids, nonsteriodal anti-inflammatory drugs (NSAIDs) or a corticosteroid–antibiotic compound has been shown to reduce post-treatment pain (Harikaran Jayakodi).

Factors interfering in the repair: Seltzer (Seltzer, 1988), (1988) correlates the local and systemic factors affecting the endodontic repair process, and suggests that the failure of the endodontic treatment may be beyond the dentist's control. Local factors include: infection; hemorrhage, tissue injury; occlusion of the blood supply; and presence of foreign bodies. Systemic factors include: nutrition; stress; state of chronic debilitation; hormones; vitamin intake; dehydration; and age. Therewith, this review also aims to discuss the association between some systemic conditions, such as diabetes mellitus, hypertension, and osteoporosis, and the periapical healing process of endodontically treated teeth.

Therapeutic factors that affect the repair process

Biochemical preparation: Root canal shaping is an important step in endodontic therapy to achieve the apical healing and the cleaning and modeling of the root canal system. However, the complex root canal anatomy, associated with the presence of curvatures and ramifications, the shape, and the position of the apical foramina, can interfere and hinder the root canal shaping and cleaning (Peters, 2004). Therewith, even with the improvement on the biomechanical preparation of root canal system using NiTi instruments, bacteria can survive and grow inside root canal systems or on apical biofilm (Rôças, 2013; Tewari, 2016 and Estrela, 2014), compromising the periapical tissue repair. Therefore, the complete repair depends on the association of an effective irrigating solution, intracanal dressing, and root canal filling to the mechanical preparation.

Irrigating solutions: Irrigation has a key role in successful endodontic treatment. Although hypochlorite is the most importantly used irrigating solution, no single irrigant can accomplish all the tasks required by an optimum irrigation solution (Haapasalo, 2010). The use of a negative apical pressure irrigation device can result in a significant reduction of postendodontic pain levels in comparison to conventional needle irrigation (Gondim, 2010). The persistence of bacterial infection following root canal preparation reveals the limitations of the irrigating solutions, such as sodium hypochlorite (NaOCl) and chlorhexidine (CHX). These solutions can only reduce the microbial population and, therefore, cannot entirely eliminate it. The sanitization process consists of the disinfection and enlargement of the root canal

via the action of sodium hypochlorite and the instrumentation techniques of the root canal, respectively. Furthermore, these protocols reduce the remaining microbiota, which improves the efficacy of the intracanal dressing and increases the success rate of the endodontic treatment (Gorduysus, 2011).

Intracanal dressing: The biological and antimicrobial action of calcium hydroxide is based on its dissociation into calcium and hydroxide ions, and on the action of these ions on tissues and bacteria (Farhad, 2005). Calcium hydroxide induces the deposition of a hard tissue bridge on the pulpal and periodontal connective tissue (Holland, 2003). Its action on connective tissue (pulpal and periodontal tissues) stimulates mineralization from the significant involvement of alkaline phosphatase and fibronectin (Holland, 2003 and Mizuno, 2008). The challenges affecting a successful root canal preparation include the following factors: complex anatomy; number of canals; curvatures; root canal ramifications; shape; and position of apical foramina, which complicates cleaning (Peters, 2004). Therewith, to achieve a complete root canal cleaning, an intracanal dressing must be used. Thus, the biological properties of calcium hydroxide, as well as its antimicrobial capacity to induce the deposition of a hard tissue, promoting a better repair, make it the intracanal medication recommended during the RCT.

Root canal filling: An ideal root canal sealer must have adequate physical, chemical, and biological properties (Gatewood, 2007 and Saxena, 2013). Several factors can affect the success of RCT, including the type and composition of sealer utilized (Gatewood, 2007; Saxena, 2013; Jitaru, 2016). The presence and release of substances from the sealers can cause different reactions when in contact with tissue (Saxena, 2013). Furthermore, even with the use of biocompatible sealers, which are capable of inducing mineralization, complete repair is only possible with the disinfection of the root canal system. Therefore, an improved repair process following RCT is promoted by the complete cleaning of the root canal, as well as by the use of an intracanal dressing, such as calcium hydroxide. Reducing the immune response to implanted biomaterials may be achieved by choosing materials that are intrinsically immune-inert, or modifying material properties to prevent recognition by the immune system (Ryan).

Apical limit of obturation: Systematic reviews have shown that root canal preparation and obturation inferior to the radiographic apex (root canal obturation at 1-2 mm inferior to the apex) were associated with a better prognosis (Schaeffer, 2005). However, even the use of biocompatible materials, such as MTA, when used as filling beyond the limit of the apical foramen, showed unsatisfactory results (Holland, 2007) this suggested that overfilling should be avoided.

Expansion of the apical foramen: Apical patency is an important factor determining the success of endodontic treatment. Root canal cleaning with the use of flexible files is recommended for the endodontic treatment of necrotic teeth; additionally, the apical constriction is maintained. This procedure, which is also referred to as apical patency, is common; it prevents the compaction of dentin chips into the foramen and helps the local elimination of microorganisms that inhibit the process of repair following endodontic treatment. However, studies on canine teeth with periapical lesions showed that optimal results were obtained when the apical foramen was expanded to a greater extent than the patency instrument (Borlina, 2010).

Endodontic infection and general health: There is also concern for the consequences of apical periodontitis and its treatment sequels in relation to other medical conditions. Focal infection originally implied dissemination of pathogens from the focus to remote part of the body, where secondary disease arose. Thus, special consideration must begiven to patients who are being treated with immunosuppressants, or otherwise have compromisedimmune systems (Dag Ørstavik and Thomas Pitt Ford) A number of the blood dyscrasias, notably leukemias, are associated potentially serious sequels to apical periodontitis: infection spreads easily and may require extensive antimicrobial therapy. A special case is presented by the irradiated patient: the high incidence of osteoradionecrosis after oral surgical procedures places high demands on effective, conservative treatment of endodontic conditions. Moreover, smoking has been shown to have an adverse effect on marginal periodontitis and wound healing; the effect of smoking on apical periodontitis has largely been overlooked (Dag Ørstavik and Thomas Pitt Ford).

Systemic factors that affect the periapical repair process

Menopause/Osteoporosis: The longer life expectancy of elderly individuals raises a concern for both the quality of life and the prevention of age-related diseases. In this context, an increase in the prevalence of bone fracture because of advanced age has been observed (Childs, 2017), particularly in post-menopausal women; this is a result of the decreased concentration of estrogen. Osteoporosis and apical periodontitis are two diseases that involve bone resorption. Studies have shown a significant correlation between these two diseases (Sultan, 2011 and Xiong, 2007), showed that the condition of apical periodontitis is aggravated by an estrogen deficiency. Low estrogen concentration also promoted an increase in the resorptive activity of the alveolar process in rats (Xiong, 2007 and Gomes-Filho, 2015).

Hypertension: The relationship between hypertension and calcium loss in bones has been shown in clinical and experimental studies (Gealh, 2014 and Tsuda, 2001). Likewise, the alteration in the activity and differentiation of bone cells observed in patients has been related to the incidence of hypertension (Landim de Barros, 2016). It has been correlated with elevated blood pressure, incidence of dental problems such as periodontitis, high rate of implant loss due to defects in the process of osseointegration (Alsaadi, 2008), and difficulties in bone healing following tooth extractions. Periodontal disease and chronic apical periodontitis showed similar inflammatory processes. Furthermore, patients with systemic diseases may have a reduced resistance to bacterial infection and tissue repair (Manrique, 2012). Periapical lesions occur as an inflammatory response to infection and, along with hypertension, can lead to vascular injury and inflammation (Sasaki, 2016).

Diabetes: The oral complications of uncontrolled diabetes mellitus include xerostomia, infection, poor healing, increased incidence & severity of caries, candidiasis, gingivitis, periodontal diseases & burning mouth syndromes (Lamster, 2008). Diabetics who present for endodontic treatment, particularly those with periradicularpathosis may have increased preoperative symptoms and should be treated with effective antimicrobial root canal regimens (Moksha Nayak).

The relationship between endodontic infections and the interaction with systemic diseases is not clear. Hyperglycemia elevates the levels of systemic inflammatory markers48 and alters the various functions of the immune system (Martins, 2016 and Shetty, 2008), including the release of inflammatory mediators. Cintra, *et al*. (Tard, 2015), correlated the serum levels of interleukin-17 (IL-17) and the infiltration of neutrophils in the presence of apical periodontitis and/or periodontal disease in diabetic rats. They found that the comorbidity of both diseases increased the serum levels of IL-17 regardless of the diabetic condition. Furthermore, an increase in the neutrophil population was observed in diabetic rats. t has been stated that PD can have a significant impact on the metabolic state in diabetes. The presence of periodontitis increases the risk of worsening of glycemic control over time (Montoya-Carralero, 2010). The activation of the inflammatory pathway in immune cells (monocytes or macrophages), endothelium cells, adipocytes, hepatocytes and muscle cells could promote an increase in the overall insulin resistance, altering the metabolic control in patients with both type 2 diabetes and chronic apical periodontitis.

Role of dietary factors in immune modulation: Nutritional factors can influence immune functioning in many ways and at many levels. It is therefore important to consider the immunological relevance of effects observed. There is evidence that diet may affect the pathogenesis of these diseases. The most promising candidates are the n-3 LCPUFA, good sources of which are fish oils and oily fish such as mackerel, herring, salmon or fresh tuna. LCPUFA in the cell membrane can serve as a source of tissue hormones such as prostaglandins and leukotrienes. When these are derived from n-3 LCPUFA, they exert anti-inflammatory effects. They also change the pattern of signalling molecules like the cytokines, which are involved in the pathogenesis of chronic inflammatory diseases. There is further evidence that vitamin C, vitamin E, selenium, carotenoids and flavonoids have an anti-inflammatory potential. Higher intakes of vitamin D could improve resistance to infections as well as immunoregulatory processes. Dietary factors that influence immune responses include total energy intake (both as it pertains to malnutrition and to obesity and dieting), total fat intake, the types of fatty acids ingested (especially n-3 LCPUFA), several vitamins (especially vitamins A, D, E, B6 and C), carotenoids, flavonoids, trace minerals (especially zinc and selenium), prebiotics and probiotics. Vitamin D has important biologic effects on glucose homeostasis, insulin release and response, and is considered to play a role in the pathogenesis of diabetes. Vitamin D can also influence the alveolar bone formation and inflammatory reactions in periradicular tissues. Hence they hypothesised that intake of Vit D may help in treating apical periodontitis in diabetic (Su, 2010).

Immune modulation by systemic therapy: Systemic drugs are analgesics, steroids, and antibiotics. NSAIDs provide an analgesic but probably little-to-no anti-inflammatory effect in these acute situations. For severe pain, a combination approach is most effective. An opioid, such as tramadol, codeine or oxycodone, and a non-steroidal agent seem to work in tandem. One combination, flurbiprofen (100mg loading π50mg each 6 h) and tramadol (100mg each 6 h) was shown to be effective in managing pain in emergency patients (Doroschak, 1999). Steroids, administered in a single dose (e.g. 4–6mg of dexamethasone) may also be of benefit (Leisinger, 1993). This would be to control a presumptive immune-mediated hypersensitivity reaction, although this mechanism has not been confirmed in flare-up patient. Some dental treatments may result in postoperative pain causing patient discomfort. The pain may arise due to either an endodontic (mostly) or a periodontal cause. Even though the endodontic pain is more common, differentiation between periodontal and endodontic origin pain has to be well established to have accurate diagnosis, which leads to proper management of any dental pain (Talal, 1969). Postendodontic pain represented with highest values after 6 hours of treatment, and reduced to almost nil after 1 week (Talal, 1969). According to previously published data, pulp therapy and root canal treatment (RCT) induce more frequent and more severe postoperative pain than do other dental operative procedures (Levin, 2006). The immune response has the potential to cause extensive secondary damage; however, more recent approaches have attempted to modulate the immune response in a manner than can more effectively promote regeneration at the site of injury. The beneficial effects of the immune response on regeneration may be retained using localized delivery systems, which do not impact the entire immune system and have the potential to selectively recruit specific immune cells or create a local anti-inflammatory microenvironment that influences the phenotype of infiltrating cells (Ryan).

Analgesics: In dentistry, the drugs employed in pain prevention and control includes local anesthetic solutions, and the so-called analgesic and antiinflammatory drugs (Andrade, 1999). Tortamano and Armonia (2001) classified the analgesics in three groups: 1. Centrally acting analgesics (opioids); 2. Peripherally acting. Jayakodi *et al*. (2012) affirmed that in case of pain of endodontic origin, patients should be treated with non-opioid analgesics; however, if the pain is not controlled, opioid analgesic must be used. According to Andrade (1999), in elderly patients, the use of either paracetamol or dipyrone is recommended for mild to moderate pain control because they do not provoke gastric irritation and interference in hemostasis. In children, the prevention in mild to moderate pain control, either paracetamol or dipyrone solutions is recommended, as drops. Similarly, these aforementioned drugs can be used in pregnant women, respecting the limit of three daily dosages, at four-hour interval, restricted by time. As the pulp is at irreversible phase, drugs are ineffective and administering analgesics is worthless. The most adequate and effective pain management is to access the root canals. As the patient is at transitional phase (from acute reversible to acute irreversible pulpitis), analgesics are effective (Andrade, 1999; Haddad, 2007 and WANNMACHER, 2007). Andrade (1999) emphasized that analgesics can be administered both in cases of pulp necrosis without periapical involvement, after accessing root canal and irreversible pulpitis which mild to moderate pain is already expected and can be prevented. Analgesics together with anti-inflammatory drugs have been mainly indicated in cases of endodontic emergency cases such as acute pericementitis (CUNHA, 2013 and Raldi, 2002). According to Andrade (1999) (Haddad, 2009), it is worth prescribing analgesics for postoperative pain control after canal instrumentation because the latter is an invasive intervention at greater risk of provoking pain. In acute apical periodontitis of bacterial origin, to prescribe analgesics/anti-inflammatory drugs at 24/48 after the removal of the septic-toxic content inside root canal provides greater comfort to patient and stops the events following the acute phase (Tortamano, 2001). Andrade (1999) (Andrade, 1999), pointed out that acute dentoalveolar abscess

cases should be treated by dipyrone or paracetamol for pain control.

Anti-inflammatory drugs: Inflammation is the body's defense response against different injury types: physical, chemical, and biological (Tortamano, 2001). Andrade (1999) (WANNMACHER, 2007), divided anti-inflammatory drugs into two groups: corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs). One approach to inducing an anti-inflammatory immune phenotype is to directly deliver corticosteroids into the local microenvironment to promote regeneration (https://www.aae.org/specialty/wpcontent/uploads/sites/2/2017/07/endodonticdiagnosisfall2013.pdf).Both betamethasone and dexamethasone are the corticosteroids of choice for dental use, through systemic route, because they have an action power 25 times greater than that of hydrocortisone, the standard drug of corticosteroids. Moreover, betamethasone and dexamethasone exhibit longer plasmatic half-life enabling their use at single preoperative dosage. Similarly, NSAIDs can be employed as adjuvants to clinical procedures for pain control in cases that acute inflammatory events are already installed, such as pericementitis, especially those from diclofenac sodium and potassium (Andrade, 1999). Chemokines are responsible for inducing recruitment of immune cells to specific sites in the body. The chemokines CXCL8/IL-8, CCL2/MCP-1, and CXCL10 are crucial in the recruitment of PMNs, monocytes, and T cells respectively. Delivery of nonsteroidal anti-inflammatory drugs (NSAIDs) has reduced IL-8 and PMN levels while not significantly reducing MCP-1 and monocyte levels (Ryan). Localized delivery can quickly and directly influence the phenotype of infiltrating immune cells, preventing the up-regulation of inflammatory cytokines and thereby creating a localized regenerative microenvironment (Ryan).

Anxiolytics: Anxiolytics or psycholeptics are drugs causing soothing effects, resulting in sleepiness. These drugs may act in agitation, excitability, anxiety, depression, apprehensiveness, psychosis, and neurosis state (Nanete de Menezes Silva, 2014). According to Haddad (2007) (Tortamano, 2001), anxiolytics are indicated in longer dental procedures, especially those performed in patients exhibiting heart diseases, diabetes, behavioral barriers and/or convulsive neurological disorders (epilepsy), and eventually in individuals with cerebral palsy and mental disabilities. Andrade (1999) (Haddad, 2007), emphasized among the benzodiazepine group: diazepam, lorazepam, bromazepam and cloxazolam. Haddad (2007) [110] still included in this group midazolam, which in addition to the anxiolytic effect has hypnotic action (induction to physiologic sleepiness). The protocol use for diazepam and bromazepam is single dosage administered 1 hour before appointment, through oral route. Lorazepam should be taken 2 hours before appointment. In extremely anxious patients, the dentist can prescribe one dosage at the night before the appointment, aiming at providing a calmer sleep (Haddad, 2007).

Antibiotics: Particularly, a history of infective endocarditis, congenital heart disease, rheumatic heart fever or the presence of an artificial heart valve or othersusceptible implants may necessitate the implement tation of an antibiotic regimen in conjunction with the endodontic procedures (Dag Ørstavik and Thomas Pitt Ford). Typical bacterial dental infection, either periodontal or periapical, is currently considered as mixed infection with involvement of aerobic, facultative anaerobic, and restricted anaerobic microorganisms. Rarely, when intracanal procedures of chemicalmechanical preparation and intracanal medication are not enough to eliminate the infection agent then antibiotics can be used to control persistent signs and symptoms, such as persistent exudates. Amoxicillin 875 mg, soluble tablets, at every 12 hours; amoxicillin 500 mg capsules at every 8 hours are the antibiotics of choice, (Nanete de Menezes Silva1 Domingos Alves dos Anjos 2014). Although antibiotics are widely used in treating a localized abscess (Yingling, 2002), prospective clinical trials show they are of no benefit for reducing postoperative pain or risk of developing a flare-up (Fouad , 1996 and Henry, 2001). However, they may be of help if there is a diffuse, rapidly spreading cellulitis into fascial spaces.

Cryotherapy: It is a relatively new form of treatment in which the body is briefly exposed to very cold temperatures in order to promote healing and other therapeutic results. The basic technique of cryotherapy stresses rapid cooling, slow thawing, and repetition of the freezing process to maximize tissue destruction (Henry, 2001). It will reduce the local blood flow by vasoconstriction and therefore, the local inflammatory reaction, swelling, and heat experience, and also will slow the conduction of nerve signals, potentially reducing pain transmission (Kullenberg, 2006). Some studies have demonstrated that cryotherapy minimizes secondary hypoxic injury through the reduction of cellular metabolism and injury area (Merrick, 1999). In dentistry, cryotherapy has been used after intraoral surgical procedures, such as periodontal surgery, extractions, and implant placement, and was found to be effective in reducing swelling and pain (Laureano Filho, 2005). One way to apply cryotherapy to the inflamed periradicular tissues is by intracanal irrigation with a cold substance after flaring the root canal system. This has been proven to be an easier task when using a negative pressure irrigation system, such as the EndoVac system (Schoeffel, 2008). The intracanal cryotherapy eliminated postendodontic pain clinically. Negative pressure reduced postendodontic pain after 6 hours of treatment (Talal Al-Nahlawi, 1969). The outcome of this study indicated that the use of intracanal cryotherapy technique with negative pressure irrigation eliminates postendodontic pain after single visit RCTs (Talal Al-Nahlawi, 1969). Cryotherapy has been used for pain relief, such as sports injuries, runner's knee, tendonitis, sprains, arthritis pain, pain and swelling after a hip or knee replacement, to treat pain or swelling under a cast or a splint, and lower back pain (Saini, 2015).

Mesenchymal Stem Cells (MSCs): Currently, several cellular approaches for the treatment of oral and dental diseases are emerging that relate to inflammation modulation. Notably, recent research has identified the ability of mesenchymal stem cells (MSCs) to modulate inflammatory processes. This immunomodulatory ability has been shown to occur as a result of cell-cell contact between MSCs and immune system cells, which results in the secretion of TGF-b and indolamine-2,3-dioxygenase-1, which can dampen the inflammatory response (Paul). Mesenchymal stem cells (MSCs) can be isolated from bone marrow and expanded *in vitro* to develop into a range of tissues, such as bone, cartilage, and fat. The delivery of MSCs has been employed to enhance regenerative processes such as wound healing and neural repair often through the secretion of trophic factors. However, these cells have also been reported to modulate the immune system in a range of applications, and this modulation may contribute to improved tissue formation (Ryan).

Antioxidants: Free radicals are defined as "any chemical species capable of independent existence that contains one or more unpaired electrons". Reactive oxygen species (ROS) and Reactive nitrogen species (RNS) are free radicals which are associated with the oxygen atom (O) or their equivalents and have stronger reactivity with other molecules, rather than with O2. Generally, ROS/RNS are generated as by-products of cellular metabolism and ionizing radiation, usually indicating the following four species: superoxide anion (O2 -), hydrogen peroxide (H2O2), hydroxyl radical (OH), and singlet oxygen (O2). The antioxidants can endogenous or obtained exogenously as a part of a diet or as dietary supplement. Humans have developed highly complex antioxidant systems (enzymatic and non-enzymatic), which work synergistically, and together with each other to protect the cells and organ systems of the body against free radical damage (Ergul Belge Kurutas, 2016). Antioxidants may represent a class of molecules that may have utility in regulating dental tissue inflammation while enabling regenerative events. Interestingly, dental resins supplemented with the antioxidant N acetyl - cysteine may modulate the activation of the key NF-kB pathway and subsequently limit the cycle of chronic inflammation (Yamada, 2008). The most efficient enzymatic antioxidants contain glutathione peroxidase, catalase and superoxide dismutase. Non-enzymatic antioxidants include Vitamin E and C, thiol antioxidants (glutathione, thioredoxin and lipoic acid), melatonin, carotenoids, natural flavonoids, and other compounds (Ergul Belge Kurutas, 2016).

Probiotics: Probiotics are live bacteria that confer a health benefit to the host.Primary infections of the necrotic pulp tissue are generally composed of a mixed bacterial community dominated by anaerobic Gram-negative bacteria. Enterococcus faecalis appears to be highly resistant to the medicaments used in the treatment, and it is one of the few microorganisms shown in vitro to be resistant to calcium hydroxide due to its proton pump. Enterococcus faecalis establishes an endodontic infection and maintains a periradicular inflammation due to its virulence factors (Aarti A Bohora), Probiotics show a potential in root canal therapy. If probioitcs are effective against endodontic pathogens, they can be potentially used as intracanal medicaments. This will be a novel concept of introducing bacteriotherapy in endodontics and replacing pathogenic bacteria by healthy bacteria, normal flora (Aarti A Bohora).

Epigenetic regulating molecules: Epigenetic regulating molecules, such as his tone deacetylase inhibitors, also show promise for therapeutic application. A recent review highlighted the current knowledge of their mode of action, which involves DNA modification, and their therapeutic usefulness in non dental areas. In particular, it emphasized their anti-inflammatory properties and ability to promote differentiation and mineralization events necessary for bone engineering (Prindeze, 2012).

Low-level laser therapy (LLLT): The mechanism by which LLLT is proposed to work is via its action on mitochondrial cytochrome C oxidase. The absorbance of light by this molecule potentially leads to its dissociation from nitric oxide, which then allows cytochrome C oxidase to rebind oxygen and re-enter respiratory chain activity leading to adenosine triphosphatase synthesis and increased cellular activity. Notably, nitric oxide levels increase during inflammation and hence may ''clog up'' mitochondrial function and metabolism. Work from other fields has now shown that the application of LLLT may be beneficial in the treatment of inflammatory diseases (Prindeze, 2012). Combined, these data now suggest that the application of LLLT at the appropriate wavelength and power could be used to modulate dental pulp inflammation while promoting repair events.

Conclusion

The challenges affecting the healing process of endodontically treated teeth include control of the inflammation of pulp or infectious processes and simultaneous neutralization of unpredictable provocations to the periapical tissue. Along with these factors, one must understand the local and general clinical conditions (systemic health of the patient) that affect the outcome of root canal treatment prediction. The appropriate application of these techniques to modulate host response has the potential to turn the immune response into an asset for regeneration, leading to the differentiation of cells toward a more regenerative and less inflammatory phenotype. At present, there are many gaps in knowledge concerning periapical inflammation, particularly with respect to the host responses, and their modulation by the immune and neural systems. Hence, there is a great need of research work to develop an effective therapy that can alleviate the clinical symptoms resulting even after an effective root canal treatment.

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