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POTENTIAL COMPLICATIONS OCCURING AS A RESULT OF INCIDENTAL DETECTION OF UNTREATED ASYMPTOMATIC APICAL PERIODONTITIS. REVIEW OF LITERATURE.

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Abstract

The incidental detection of asymptomatic apical periodontitis prompts the question of whether or not this lesion should be treated. Arguments favoring treatment are that the inflammation may cause pain in the future, may enlarge, or may negatively affect the host's resistance. Reasons for not treating may be that treatment weakens the tooth, may cause iatrogenic damage, and that

treatment is expensive and burdensome for the patient and does not lead to complete recovery in all cases. A lack of scientific evidence exists to support either option, whether it involves treating the lesion or not.

Keywords- Periodontitis, incidental detection, inflammation

Introduction:

Pulp disease is considered to contribute to apical periodontitis, which often defines different periapical conditions and various pathological disorders and conditions (Nair 1997). When a tooth is affected by a microbial infection that is persistent in its root canal system, the periradicular tissues develop inflammation that causes apical periodontitis (Kakehashi et al., 1965; Sundqvist, 1976).

Around 60% of people across the world are likely to be affected by the prevalent disease of primary apical periodontitis (Eriksen, 1998). The main source or origin of apical periodontitis is when the necrotic root canal becomes infected, which is defined as a primary endodontic infection (Siqueira 2002). Apical periodontitis is revealed in biofilms by a mix of bacterial species but is dominated by obligate anaerobic bacteria within the root canal system when infection is first noticed (Ricucci & Siqueira 2010).

The human body's response to these primary infections could show clinical manifestations that differ and relate to apical periodontitis (Rôças et al. 2011). There is insufficient understanding of how symptoms of this disease develop or the associated factors that could be linked, and apical periodontitis could be acute (symptomatic) or chronic (asymptomatic). Although research investigations have attempted to identify links between symptoms and various bacterial species to establish a correlation (Sundqvist 1976; Sassone et al. 2008), other research has shown that in asymptomatic examples of this disease, the same species are present and at higher levels of prevalence (Siqueira & Rôças 2005).

Findings show that if apical periodontitis persists after a root canal treatment, the therapeutic and aetiological situation becomes more complex compared to patients with teeth affected by the disease who have not received previous dental treatment (Nair 2006). Additionally, a wider range of treatments and a broader aetiological spectrum are possible for persistent apical periodontitis in patients who have not received root canal treatment (Nair 2006).

Microbial factors are the main source of persistent inflammation after root canal treatment (Nair 2004). These factors contribute to the persistence of infection when root canal treatment fails to reach the bacteria or when the bacteria demonstrate resistance (Siqueira & Rôças 2008). Candida albicans and Enterococcus faecalis are bacterial species regularly discovered in root-filled teeth (Peciuliene et al., 2001; Waltimo et al., 2003). When teeth undergoing root canal treatment exhibit apical periodontitis, we can characterize the microbial flora as a monoinfection, dominated by Gram-positive microorganisms, with half of the bacteria being obligate anaerobes and the other half being facultative anaerobes (Molander et al., 1998; Sundqvist et al., 1998).

To summarize these findings, when the root canal system shows persistent infection, the apical tissues develop an inflammatory disorder known as apical periodontitis. Microbial factors are believed to be the primary cause of persistent inflammation following root canal treatment, and it's crucial to manage and eradicate the prevalent apical periodontitis to preserve healthy dental tissues, as it significantly impacts patients' quality of life. The following section analyzes apical periodontitis aetiology and its association with systemic health to discover what effective treatments could be adopted to eliminate asymptomatic apical periodontitis.

Apical periodontitis: aetiology

When apical periodontitis is persistent, this could be due to leaking permanent or temporary restorations, insufficient instrumentation, missed canals, poor access, cavity design, or inadequate aseptic control (Sundqvist et al. 1998). The root canal system is anatomically complex, and there are sections that, with current techniques, materials, and instruments, cannot be obturated and debrided, so that, radiographically, some lesions could persist despite carrying out clinical procedures that are appropriate (Nair et al. 2005). Other findings have shown that post-treatment of the lesion could be affected by sources located inside the inflamed periapical tissue, so that factors could be associated with delayed healing that are not linked with the root canal system (Sjögren et al. 1988).

Microbial causes:

Microbial causes can be intraradicular infection as a result of microorganisms in the apical root canal or extraradicular infection caused by actinomyces in the form of perical actionmyosis.

Intraradicular infection:

The findings of research into root canal systems when 66 specimens were studied discovered bacteria in 14% of the sample, where this histobacteriological study (Andreasen & Rud 1972) used specific bacterial stains and step serial sectioning. These findings contrast with a later investigation of root canal systems when 86 specimens of endodontic surgery were studied, and in 63% of the sample, bacteria and debris were revealed, but the researchers noted that these could not be regarded as agents that would potentially cause infections (Lin et al. 1991). Nair et al. (2005) reported that when root canal treatment involved filling, irrigation with NaOC1, and instrumentation that was carried out in one treatment session, of the 16 root-filled mandibular molars, 14 displayed residual infection within the mesial roots. In addition, microbiological techniques were used in another study to confirm that in teeth with root canal treatment showing apical periodontitis, intracanal fungi were present (Waltimo et al. 1997). Periapical healing could also be negatively affected when the deepest parts of dentinal tubules are infected, so endodontic reinfection could be caused by this reservoir of infected bacteria, described as intraradicular infection (Peters et al., 1995; Love & Jenkinson, 2002).

Extraradicular infection:

The genera Propionibacterium and Actinomyces cause actinomycosis, which is an infectious disease affecting animals and humans that is granulomatous and chronic (McGhee et al., 1982). In other research, a sample population of 79 cases of treatments showed actinomycotic involvement in this microbiological control study (Byström et al. 1987). Other findings report that in a study of 45 lesions, two cases showed that actinomycotic colonies were present from a histological analysis (Nair & Schroeder 1984).

Following appropriate root canal treatment, actinomycotic organisms can still contribute to continuing inflammation at the periapex, as these organisms are able to establish extraradicularly, so that in the field of endodontics, periapical actinomycosis is a critically important factor (Sundqvist & Reuterving 1980; Sjögren et al. 1988). When the periapical tissue of teeth does not show the expected response to endodontic treatments that are non-surgical, P. proprionicum and Actinomyces israelii are often characterized and isolated (Happonen 1986; Sjögren et al. 1988).

Although at the root apex, inflammation can be sustained extraradicularly by actinomycotic organisms, some bacterial species have been described at extraradicular locations of lesions that are unyielding to endodontic treatments and defined as asymptomatic periapical lesions that are inflammatory by Tronstad et al. (1987). Therefore, at the apical foramen of teeth, microorganisms are often found with apical periodontitis that is persistent (Nair et al. 1999).

Various research reports indicate that viruses are present within inflamed periapical tissues, which suggests an etiopathogenic association with apical periodontitis (Sabeti & Slots 2004).

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Non-microbial causes:

Cystic apical periodontitis:

Findings suggest that in 16 block biopsies that were histologically reliable for a study of apical periodontitis that was persistent, 13% showed cystic specimens (Nair et al. 1999), but when compared with a large study of primary apical periodontitis lesions, this was greater than 9% of cystic specimens in the larger study (Nair et al. 1999). Table 1 shows the findings of human apical periodontitis studies into prevalence of radicular cysts.

Reference	Cysts %	Granuloma %	Others %	Total lesions (n)
Sommer et al. (1966)	6	84	10	170
Block et al. (1976)	6	94	-	230
Sonnabend & Oh (1966)	7	93	-	237

Winstock (1980)	8	83	9	9804
Linenberg et al. (1964)	9	80	11	110
Wais (1958)	14	84	2	50
Patterson et al. (1964)	14	84	2	501
Nair et al. (1996)	15	50	35	256
Simon (1980)	17	77	6	35
Stockdale & Chandler (1988)	17	77	6	1108
Lin et al. (1991)	19	-	81	150
Nobuhara & Del Rio (1993)	22	59	19	150
Baumann & Rossman (1956)	26	74	-	121
Mortensen et al. (1970)	41	59	-	396
Bhaskar (1966)	42	48	10	2308
Spatafore et al. (1990)	42	52	6	1659
Lalonde & Luebke (1968)	44	45	11	800
Seltzer et al. (1967)	51	45	4	87
Priebe et al. (1954)	55	45	-	101

Apical periodontitis lesions: incidence of radicular cysts (Nair 2006).

Radiographs cannot be used on their own to diagnose differentially between cystic and non-cystic lesions to determine apical periodontitis (Baumann & Rossman 1956, Mortensen et al. 1970). A periapical pocket cyst could heal following orthograde root canal treatment, as infectious material is removed and filling prevents reinfection (Simon 1980, Nair et al. 1996). However, a cyst defined as true could maintain itself (Nair et al. 1993), which is determined by its quality of being independent of the absence or presence of irritants within the root canal system and its tissue dynamics (Simon 1980).

Cholesterol crystals:

When host cells, such as circulating plasma lipids, macrophages, plasma cells, lymphocytes and erythrocytes, disintegrate they release cholesterol crystals that precipitate and accumulate (Shear 1963), and these cholesterol crystals could be a significant aetiological factor for chronic inflammation that is non-resolving (Nair et al. 1998). Therefore, a foreign body reaction could be induced by these crystals due to their accumulation of giant cells and macrophages (Sjögren et al. 1995).

Gutta-percha:

Contaminated gutta-percha was shown in one biopsy in analysis by correlative light and electron microscopy of surgical block biopsies of nine asymptomatic apical periodontitis lesions (Nair et al. 1990b). Talc contaminated gutta-percha cones and other insoluble substances can be contained with root filling materials, which produce foreign body reactions if they protrude into periradicular tissues and contribute to failed treatments (Nair et al. 1990b).

Foreign bodies:

When inserted into periradicular tissues, lesions could persist as a result of vegetable food materials, cotton wool or the cellulose part of paper (Koppang et al. 1989). Humans are unable to digest the polysaccharide of plant cell walls and defence cells are unable to degrade these, so cellulose could contribute to foreign body reaction and be retained within tissues for extended periods (Siqueira 2001).

Pulses, such as leguminous seeds and plant origin food materials are often adopted in endodontics and during and before treatment procedures these materials could become lodged in the periapical tissue, which could prevent the lesion from healing (Nair 2006).

Calcium salts from periapically extruded $Ca(OH)_2$, endodontic sealants and amalgam are other materials that could become foreign bodies, and 31% of specimens from a sample population of 29 apical biopsies subjected to x-ray and histological microanalytical investigation were shown to contain endodontic sealer and amalgam components (Koppang et al. 1992).

Scar tissue healing:

Findings suggest that when endodontic treatment is shown to have failed by radiographic evidence, this could be an error due to scar tissue healing of the lesion, but periapical radiolucency often

remains unresolved (Bhaskar 1966, Seltzer et al. 1967, Nair et al. 1999).

After root canal treatment, periapical radiolucency that is persistent could be due to the following biological factors (Nair 2006).

- Lesion is healed by scar tissue processes,
- Cholesterol crystals, extruded fillings and other materials could contribute to foreign body reactions, but particularly crystalline substances of endogenous origin,
- Cystic lesions,
- Periapical actinomycosis and extraradicular infection, and
- Within the apical root canal system, intraradicular infection.

In summary, Although all these factors are important, most failed treatments of endodontic procedures are due to persistent microbial infection within the apical part of the root canal system (Nair et al. 1990a, Sjögren 1996, Figdor 2004). This forms the justification to eliminate bacteria as the principle cause and to cure the tissues to effectively treat asymptomatic apical periodontitis, so that eliminating microorganisms in the apical part and overall in the root canal system would be the main target of treatment procedures. It is extremely unlikely that treatments could fail as a result of scar tissue healing, foreign body reaction, cystic lesions or extraradicular actinomycosis (Nair 2004). Therefore, as many endodontic treatments fail due to extraradicular infections, approaches that do not adopt surgical procedures would not be justified, but would need systemic medication or apical surgery, or both procedures.

Some clinicians could diagnose asymptomatic apical periodontitis incorrectly, when scar tissue healing is present, so that it is critically important for clinicians to recognise clinical presentation of apical periodontitis to make accurate diagnosis. The following section investigates the clinical manifestations and diagnosis of apical periodontitis that could provide help to clinicians is deciding treatment procedures.

Apical periodontitis: clinical manifestations and diagnosis

When the root canal system has a bacterial infection, this has a direct association with periapical inflammation, so that clinicians need to diagnose and examine the condition of the periapical tissues and the pulp when making assessments of teeth (Abbott 2004b). Disease needs to be treated to stop this reoccurring, so that its cause should be eliminated, and an important task of clinicians is to identify this cause of disease, and for periapical and pulp diseases it is important to identify pathways that bacteria could follow to enter the root canal system, so that effective clinical management of teeth would include removing these (Abbott 2004a). Accurate diagnosis is important for clinicians and patients, so that although a root canal system that is infected is probably the cause that leads to apical periodontitis diagnosis, other causes should also be considered and evaluated (Abbott 2004b).

Periapical inflammation: pulp infection not evident

The root canal system might have no infection, but apical periodontitis could still develop, such as

the result of protrusive and lateral movements of the mandible that cause occlusal interference or premature occlusal contact, so that the periodontal ligament experiences irritation that is constant and continuous that produces inflammation, and defined as traumatic (Kvinnsland et al. 1992, Shi et al. 1997). When violent force causes a tooth to be displaced, avulsion and luxation injuries often occur and these types of trauma could contribute to apical periodontitis (Andreasen 1986).

When periodontal disease is extensive and the pocket exceeds the root apex level, periapical radiographs could incorrectly indicate apical periodontitis, when there is no root canal system infection (Lindhe et al. 2008). When this situation occurs, radiolucency is created by loss of bone lingually or labially and supporting tissues demonstrate substantial breakdown, so that apical periodontitis is suggested by the superimposition of this radiolucency over the periapical region, which is shown in Figure 1 (Abbott 2004b).

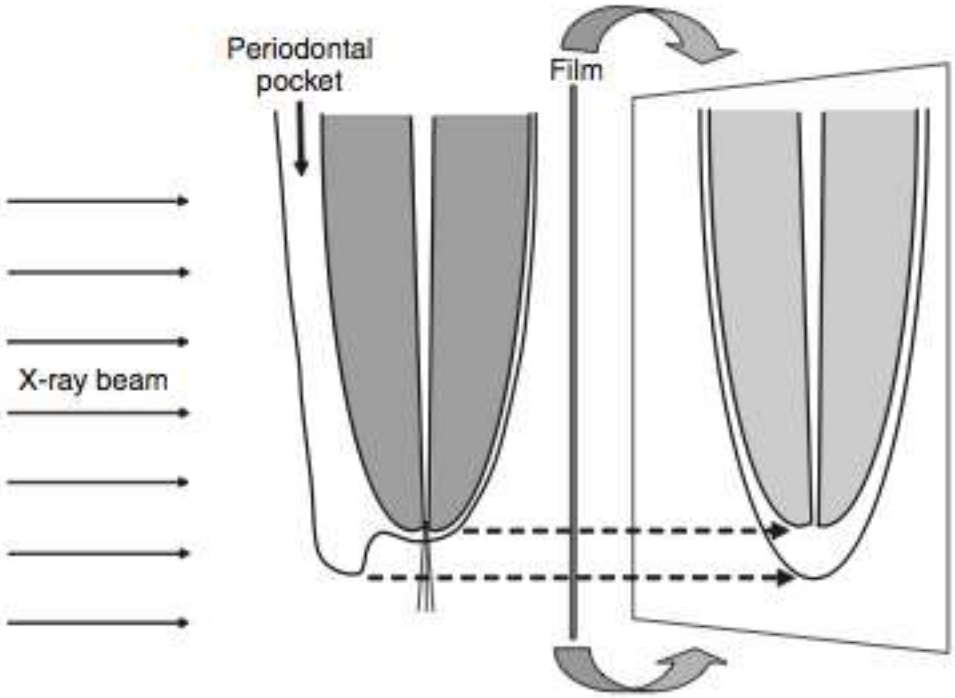


Figure 1: This shows that periapical radiolucency could be mimicked when considerable loss of labial bone is caused by a periodontal pocket. It should be noted that the nerve supply and apical blood vessels remain intact. Pulp sensibility tests are required to test and examine the tooth in detail, as a suggestion of a lesion by radiography procedures could incorrectly indicate chronic periodontitis due to infection of the root canal system and pulp necrosis (Abbott 2004b).

On rare occasions, infection of the root canal system and pulp necrosis are caused when the blood supply of the pulp is severed and the periodontal pocket involves the apical foramen, which differs to most situations of extensive periodontal disease (Langeland et al. 1974).

Asymptomatic apical periodontitis lesions: herpes viruses

There is general agreement that the pathogenesis of apical periodontitis is affected by endodontic bacteria (Marton & Kiss 2000, Siqueira Jr & Rôças 2007). Endodontic pathogens include more than 460 bacterial species that are different (Siqueira & Rôças 2009, Siqueira et al. 2011).

Previous studies have found Epstein-Barr virus (EBV) and human cytomegalovirus (MCMV) and other herpes viruses are often found within these (Slots 2004, Cappuyns et al. 2005, Slots et al. 2006). Slots et al. (2006) indicated that periodontitis is affected by herpes viruses in terms of its course and development, but these findings are challenged by Cappuyns et al. (2005). Sabeti et al. (2003) argued that the pathogenesis of both marginal periodontitis and apical periodontitis tend to be associated with herpes viral infections.

Herpes viruses can change the cellular environment and the activities of immune systems that are adaptive and innate for humans due to proteins being expressed during the latent and lytic viral life cycle (Slots 2009). Blood and bodily secretions, such as breast milk, semen, urine and saliva, of humans can contain cytomegaloviruses, which often result in infectious diseases that are serious (Cappuyns et al. 2005). During latency, human cytomegaloviruses inhabit bone marrow myeloid progenitor cells, and granulocytes, monocyte-derived macrophages, hepatocytes, mesenchymal cells, smooth muscle cells, endothelial cells and epithelial cells could be infected by human cytomegaloviruses (Cappuyns et al. 2005, Chen et al. 2009).

When immunosuppression is present in humans, the aetiology of lymphoproliferative disorders, Burkitt's lymphoma and nasopharyngeal carcinoma is associated with Epstein-Barr virus, which is also thought to contribute to infectious mononucleosis (Slots et al. 2003), where blood or oral secretions transmit this virus (Cappuyns et al. 2005). Epstein-Barr virus could infect the oropharyngeal epithelium and for latent and primary infections it could infect long lived B-lymphocytes (Slots 2005).

Jakovljevic and Andric (2014) reviewed 17 previous cross sectional studies to investigate the relationship between clinical features of apical periodontitis and HCMV and EBV messenger RNA transcripts being present, but this systematic review found no relationship that was statistically significant. Although in large size and symptomatic periapical lesions herpes viruses were common, there was no statistical significance in association with HCMV and EBV transcripts for apical periodontitis. The researchers suggest that experimental animal models could be used in further studies of this topic, as more information is needed to clarify whether the factor of herpes viruses is associated with the pathogenesis of periapical inflammation.

Therefore, although some findings indicate that herpes viruses do play a role in influencing periodontitis in terms of its course and development, other research suggests that apical periodontitis development and formation and the role of HCMV and EBV lack certainty, although often found in large size lesions and symptomatic periapical periodontitis (Sabeti et al. 2003, Slots et al. 2006). However, other research findings into asymptomatic apical periodontitis have reported that these viruses have been detected (Ozbek et al. 2013). Therefore, these findings suggest that herpes viruses could be associated with the persistence of bacteria at the site of asymptomatic

apical periodontitis and in the apical part of the root canal system, so that clinicians should advise patients of the need for clinical intervention in order to avoid exacerbation of the lesion.

Asymptomatic apical periodontitis: yeasts

Yeasts are defined as fungi, which differs to bacteria, as the genome of fungi has a membrane that surrounds its nucleus, so that fungi that includes yeasts are defined as eukaryotic organisms (Waltimo et al. 2003). The structure of the walls of fungal cells are rigid and these cells include chitin, mannan and glucan, and the cell wall absorbs carbon and nitrogen compounds for the nutrition of fungal organisms (de Hoog et al. 2000). The human body has yeasts present at different sites that are described as normal flora, such as at the perineal area, vagina and gastro-intestinal tract (Jarvis 1996).

For more than sixty years, previous studies have isolated yeasts from within root canal systems that were infected that used microbiological investigations of apical periodontitis (Slack 1953, Sen et al. 1995, Molander et al. 1998). Slack (1953) studied apical periodontitis and found that in 5% of cases yeasts existed. Nair et al. (1990a) investigated nine specimens and found microorganisms in six of these taken from therapy resistant root canal infections. An electron microscope was used in this study to evaluate these six cases further and in four cases, bacteria was revealed, and in two cases yeast-like organisms were revealed.

In summary, these findings show that for the aetiology of apical periodontitis, the complex organisms that form a community of microbes, such as yeasts, viruses and bacteria play an important role when they interact together (Sedgley et al. 2008). Therefore, again these microbes should be eradicated to prevent exacerbation and flaring-up of asymptomatic apical periodontitis.

Oral Infection: Systemic Diseases

Similarities are noted between chronic inflammatory disease of endodontic and periodontal origins in spite of the differences discussed earlier, and these similarities are addressed below:

- These inflammatory diseases share an ecological community of microorganisms or microbiota that has an association with Gram-negative anaerobic bacteria (Sundqvist 1992, Noiri et al. 2001).
- Both diseases show increased concentration of inflammatory mediators in periapical tissues of endodontically involved teeth and in gingival crevicular fluid of periodontal disease, and findings report higher systemic cytokine levels (Barkhordar et al. 1999).
- These inflammatory diseases are located in the oral cavity and defined as chronic infections (Segura-Egea et al. 2012).

Complex microfloras are associated with human periodontal and endodontal infections, where in apical periodontitis there are around 200 species (Tronstad 1992) and in marginal periodontitis there are around 500 species (Moore & Moore 1994).

The problem with apical periodontitis is that it is very common (Figdor 2002), and the increased age of humans is associated with more frequent incidents of apical periodontitis by an increase of around 61% (Jiménez-Pinzón et al. 2004). The treatment for apical periodontitis involves root canal procedures that are often combined with surgical endodontics, which should restore full health to periradicular tissues (Segura-Egea et al. 2012). Endodontic treatments in Europe account for about 41% of dental treatments (Jiménez-Pinzón et al. 2004).

The dental and medical scientific research communities have focused investigations into possible associations between systemic health and periodontal disease and chronic apical periodontitis that form the main infectious oral inflammatory processes (Segura-Egea et al. 2012). Therefore, over the previous twenty years, the possible link between periodontal disease and systemic health has been researched by various epidemiological studies (Segura-Egea et al. 2012). These investigations into links with periodontal disease have reported associations with coronary heart disease (Beck et al. 1996), as well as osteoporosis in post-menopause women (Bullon et al. 2005), respiratory diseases (Scannapieco et al. 2003), preterm-low birth weight (Marin et al. 2005), diabetes mellitus (Katz 2001, Soskolne & Klinger 2001), and acute myocardial infarction (Grau et al. 2004).

The risk factor of oral infection has been suggested for systemic diseases, and particularly apical and marginal periodontitis based on various epidemiological studies (Li et al. 2000). The following section discusses how oral infections could be linked by pathways to secondary non-oral diseases, before these systemic diseases are reviewed further.

Oral infection linked to secondary non-oral disease: pathways

Findings suggest that secondary systemic effects are linked to oral infections by pathways or mechanisms (Thoden van Velzen et al. 1984). It this thought that infection changes form, state or position from the oral cavity by metastatic spread due to transient bacteraemia, oral microorganisms that induce immunological injury that causes metastatic inflammation, and circulating oral microbial toxins that produce metastatic injury.

Metastatic infection: Transient bacteraemia can be caused by dental procedures and oral infections. Normally, the reticuloendothelial system eliminates the transient bacteraemia very quickly when microorganisms circulate through the human body after gaining entrance to the blood stream, and clinical symptoms would usually be presented as the body temperature increasing slightly (Kilian 1982, Thoden van Velzen et al. 1984).These processes change if favourable conditions for microorganisms that are circulating in the blood are found, so that after remaining at a specific site, they start to multiply over time (Li et al. 2000).

Metastatic injury: Exotoxins or diffusible proteins, such as dimeric toxins with A and B sub units and cytolytic enzymes can be produced by some Gram-negative and Gram-positive bacteria (Li et al. 2000). Findings suggest that exotoxins are poisons that are highly lethal and powerful, as they have pharmacological actions that are specific (Hammond 1992), although after cell death, when outer membranes are released, these include endotoxins that form part of these (McGhee et al. 1982, Hammond 1992). When carried by a host, Endotoxin produces many pathological

symptoms, and the composition of endotoxin is lipopolysaccharide (LPS) (Li et al. 2000).
Metastatic inflammation: When the blood stream receives a soluble antigen, this contributes to forming a macromolecular complex after reacting with a specific circulating antibody (Li et al. 2000). Therefore, at sites of deposition, chronic and acute inflammatory reactions could occur due to these immunocomplexes (Thoden van Velzen et al. 1984, Van Dyke et al. 1986). Table 1 shows non oral diseases and oral infection pathways that could be associated (Li et al. 2000).

Oral infections: Pathways	Non oral diseases that are possible
Metastatic infection: by transient bacteraemia from oral cavity	prosthetic joint infection, osteomyelitis, skin ulcer, orbital cellulitis, Ludwig's angina, lung abscess/infection, sinusitis, cavernous sinus thrombosis, brain abscess, acute bacterial myocarditis, and sub acute infective endocarditis
Metastatic injury: oral microbial toxins circulation	Chronic meningitis, systemic granulocytic cell defects, toxic shock syndrome, idiopathic trigeminal neuralgia, persistent pyrexia, abnormal pregnancy outcome, acute myocardial infarction, cerebral infarction
Metastatic inflammation: oral organisms causing immunological injury	Crohn's disease, inflammatory bowel disease, uveitis, chronic urticaria, Behcet's syndrome

Coronary heart disease:

Research findings indicate links between coronary heart disease (CHD) and periodontal disease, when bacterial infection causes localised inflammatory symptoms that lead to cytokines being released into the blood stream, which produces harmful vascular effects, and the mechanisms that link CHD with endodontic disease could be similar (Beck et al. 1996). When considering

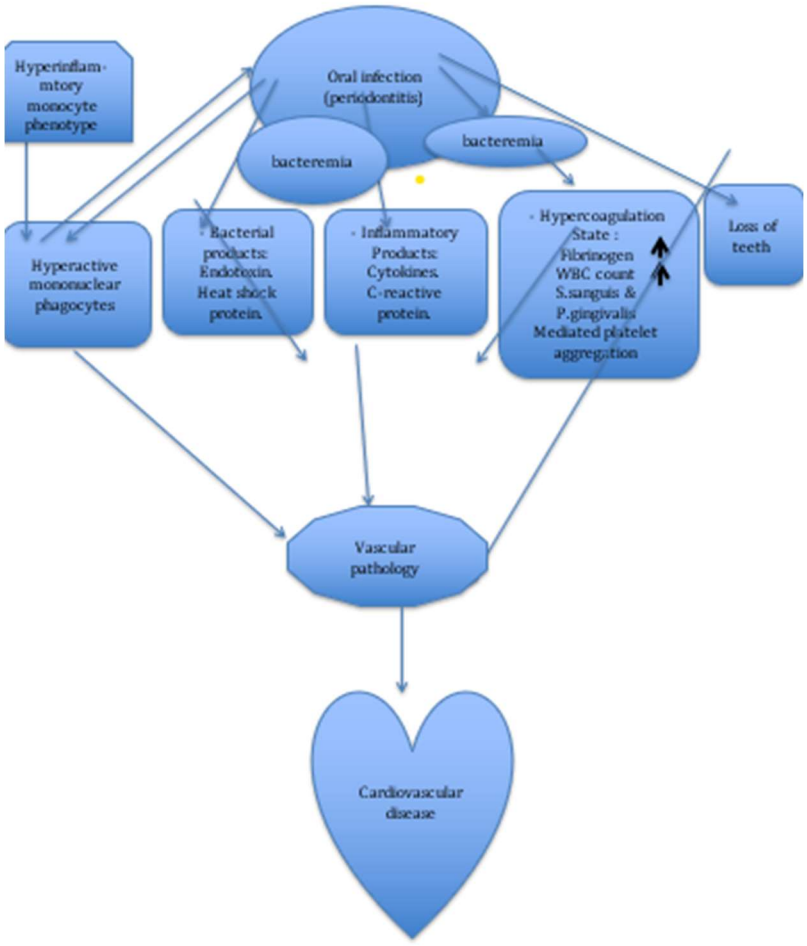
endodontic infections when Gram-negative anaerobes tend to predominate, there is a biological likelihood of associations between cardiovascular outcomes and endodontic inflammation (Sundqvist 1992), periapical granulomatous tissues and inflamed pulp show indications of producing cytokine (Miller et al. 1996, Barkhordar et al. 1999), and in endodontic patients inflammatory mediators are observed to have systemic levels that are elevated (Márion et al. 1988, Marton & Kiss 1992). However, another study challenges these findings, and finds that CHD presence and number of teeth with LEO (lesions of endodontic origin) show no relationship that is significant. This was based on a cross sectional investigation that involved a sample population of 1056 women aged 38 years to 84 years in Sweden that examined systemic health outcomes and chronic endodontic disease to discover no significant relationship (Frisk et al. 2003).

Caplan et al. (2006) carried out a Veterans Affairs (VA) Dental Longitudinal Study to examine a sample population 708 males to investigate whether CHD could develop from lesions of endodontic origin from radiographic images. These findings reported that there was a significant association between lesions of endodontic origin and CHD diagnosis for participants who were 40 years of age or younger. However, no association that was statistically significant was observed for participants who were over the age of 40 years. The researchers report that there could be a weaker relationship for older adults, because the development of CHD could be linked more strongly with other characteristics, but that this relationship does exist for all age groups. However, these findings also suggest that older people would be more healthy than those in their cohort who had died previously, so that the phenomenon of the healthy survivor could be represented in this study.

Various research findings indicate that infections are likely to influence CHD development (Mattila et al. 1998). Research investigations into CHD patients have adopted studies that are placebo-controlled, double-blind and randomised, and when patients were given antibiotic therapy, the risk of recurrent ischemic events showed a reduction, which supports the argument that there is a causal link between CHD and infections (Gupta et al. 1997, Gurfinkel et al. 1999).

The influencing factors of white blood cell (WBC) counts, association of high peripheral fibrinogen, involvement of heavy immune and inflammatory infiltrates, levels of proinflammatory cytokines that are easily detectable, and the involvement of Gram-negative species that are abundant, it appears highly likely that periodontal disease could contribute to cardiovascular disease for some humans (Kinane 1998). Both periodontal and endodontic chronic inflammatory diseases caused by the same microbiota which often associated with gram-anaerobic bacteria as mentioned earlier (Sundqvist 1992, Noiri et al. 2001). Figure 2 shows how pathways could be caused by mechanisms of periodontal disease from indirect and direct effects of oral bacteria that contribute to cardiovascular disease (Li et al. 2000). For chronic inflammatory endodontic diseases, the following pathways could be considered.

Figure 2



In summary, in most European countries, and for males and females, the main cause of hospitalisation and death is cardiovascular disease (CVD), and the cause of death from CVDs that is most common in Europe is ischemic heart disease (Nieminen & Harjola 2005). The risk factors for CHD and atherosclerosis include genetic disposition, high low-density lipoprotein (LDL) serum levels, obesity, smoking, socioeconomic status, sex, diabetes and hypertension (Wilson et al. 1987). The most significant risk factors that contribute to heart disease for young patients are family history and smoking (Graham et al. 2007). However, recent findings suggest that heart disease can be correlated with chronic inflammatory diseases that are present in patients that represent unconventional factors. Therefore, the development of non-fatal and fatal myocardial infarction has been shown in recent studies to be closely linked with haemostatic factors and activated inflammation of circulating markers (Libby et al. 2002), so that atherosclerosis could be predicted by chronic inflammatory processes, and CHD has been specifically associated with chronic oral infections (Mattila et al. 2000, Scannapieco et al. 2003). There is consistent evidence that in humans increased levels of systemic inflammation is associated with apical periodontitis, but although currently this evidence is limited, to avoid potential complications, asymptomatic apical periodontitis needs to be treated.

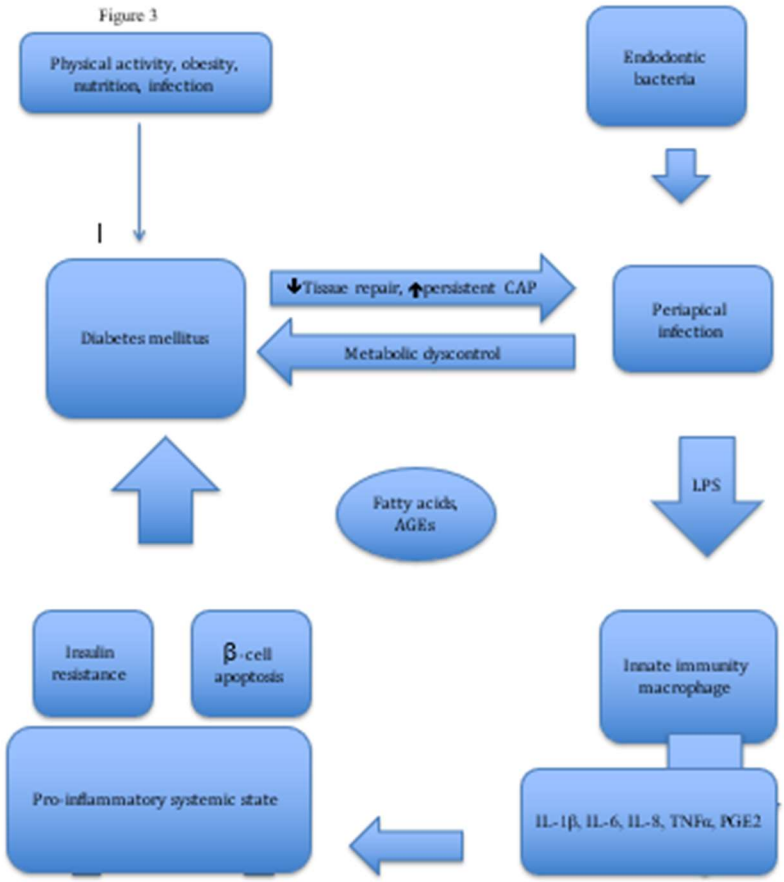
Diabetes mellitus:

When the human body presents insulin resistance in muscle and liver organs or pancreatic β-cell dysfunction this creates a deficiency in insulin secretion that contributes to a group of complex multisystem metabolic disorders known as diabetes mellitus (DM) (Segura-Egea et al. 2012). There are two types of diabetes, where type 1 diabetes involves total loss of insulin secretion due to cellular-mediated autoimmune destruction of pancreatic β-cells, and type 2 diabetes involves inability to produce sufficient insulin to overcome resistance to insulin (Segura-Egea et al. 2012). Therefore, diabetes mellitus contributes to systemic and oral manifestations (Eldarrat 2010, Al-Maskari et al. 2011), difficulties for wounds to heal (Garber et al. 2009), and hyperglycaemia (Dienelt & zur Nieden 2010). In 2011, this metabolic disorder affected around 366 million patients across the world of all ages (Wittrant et al. 2008, Al-Maskari et al. 2011, Rewers 2012).

Findings suggest that insulin resistance could be propagated or initiated by periodontal diseases (PD) that could be compared to obesity, as cytokines enhance the activation of the systemic immune response overall (Katz 2001). As chronic periapical inflammatory process is a risk factor for reduced control of glycaemia for patients with diabetes, findings suggest that this contributes to the pathogenesis of DM (Segura-Egea et al. 2012). Bender et al. (1963) indicated that patients are placed in an uncontrolled diabetic state when blood glucose rises as a result of intensification of diabetes cause by increased local inflammation, so that for diabetic patients, inflammatory periapical reactions are greater.

Infection, obesity, poor nutrition, decreased physical activity and other genetically modified environmental factors tend to influence the development of insulin resistance associated with inflammatory mediator activity linked to chronic inflammation (Pickup 2004). When apical periodontitis is caused by lipopolysaccharide (LPS) produced by anaerobic Gram-negative bacteria, this initiates intracellular pathways, such as nuclear factor kappa B (NF-kβ) on neutrophils and macrophages. This upregulates proinflammatory cytokines, such as prostaglandin E2 (PGE2), tumour necrosis factor alpha (TNF-α) and IL-1β, IL-6, IL-8 (Segura-Egea et al. 2012). These cytokines that are locally produced interact with advanced products of glycosylation (AGEs) and free fatty acids after moving into the systemic circulation that characterises type 2 diabetes (Doyle et al. 2007). For patients with chronic apical periodontitis and type 2 diabetes, their metabolic control is altered when inflammatory pathways are activated in muscle cells, hepatocytes, adipocytes, endothelium cells and monocyte or macrophage immune cells that could lead to increased overall insulin resistance (Segura-Egea et al. 2012).

Figure 3 shows how for diabetic patients, chronic periapical infection mechanism effects could be similar to mechanisms that exist between DM and PD (Tunes et al. 2010)



In summary, although an association between AP and DM is suggested by previous studies, these findings lack sufficient evidence to be conclusive. However, the review of literature presents findings that link DM with the arrest or delay of periapical repair, greater likelihood of asymptomatic periapical infections, greater size of periapical osteolytic lesions and greater prevalence of AP. Diabetic metabolic dyscontrol has also been suggested to be associated with chronic periapical disease in some previous studies (Segura-Egea et al. 2012).
These findings present justification to avoid the health of patients being compromised by treating asymptomatic apical periodontitis as a chronic oral disease, although the association between periapical inflammation and DM requires further epidemiological studies to gain a deeper understanding.

Conculsion:

Within the root canal system, microbial infection of a tooth can cause inflammatory disease of periradicular tissues that is described as apical periodontitis, which is usually caused by oral microbiota infecting the root canal system as a result of dental caries or tooth decay (Hong et al.

2013, Siqueira & Rôças 2013). The quality of life for patients is affected considerably by apical periodontitis, which is a common condition (Vengerfeldt et al. 2014). In healthy humans, infections are prevented from spreading into tissue around the apical foramen by the body's immune defence response, but apical periodontitis lesions do not heal naturally when microorganisms that caused the disease cannot be accessed by systemically administered antibiotics and immune defence systems of the body (Siqueira Jr & Rôças 2008). Therefore, dental clinicians need to consider whether to wait until the patient reports pain or other symptoms, identify if the disease becomes worse or immediately treat the asymptomatic apical periodontitis.
Dental clinicians are recommended to carry out root canal treatment by European guidelines if they observe that the dental pulp is necrotic, but do not need to use radiographs to find evidence of periapical radiolucency (European Society of Endodontology 2006). These guidelines raise the importance of removing likely sources of infection and identified infection that would be found in a necrotic dental pulp (Wesselink 2014). The outcomes of root canal treatment would remove unexpected increase in the severity of the disease for patients, such as adverse systemic effects of local inflammation and infection, or pain and swelling with apical periodontitis (Li et al. 2000).
Reasons for recommending treatment:

Increased severity of disease, signs or symptoms: When patients report sudden pain on a regular basis, dental clinicians need to investigate if this could be caused by periapical inflammation (Wesselink 2014). The pattern of frequency of chronic inflammation that produces the symptoms of pain lack clear evidence (Wesselink 2014). However, the lesion could worsen in its condition, which would justify performing the root canal treatment.
The lesion could grow: When decisions that are made between the dental clinician and the patient to not treat a lesion, then this could grow larger and affect other nearby teeth and structures within the jaw (Wesselink 2014). When these larger lesions are treated later by surgical intervention, damage to nearby structures or teeth could take place, which would be prevented if treatment was adopted at an earlier stage (Wesselink 2014). Clinical experience indicates that surgical intervention is infrequently required for chronic periapical conditions, but there is no scientific evidence to support this (Wesselink 2014).
Risks of infections and inflammation: The relationship between the markers indicating systemic diseases are present, such as C-reactive proteins and interleukins in large amounts and periapical radiolucencies was not found in some previous studies (Frisk et al. 2003, Buttke et al. 2005). Other findings report no causative correlation that is clear between systemic disorders, such as diabetes mellitus, chronic heart disease and atherosclerosis, and periapical inflammation (Löst 2006). More recent studies that offer consistent, but limited, evidence indicate that increased levels of systemic inflammation in humans is associated with apical periodontitis (Wesselink 2014). Conventional periapical radiographs have been used to diagnose all investigations of apical periodontitis, so that this association should not be discounted (Wesselink 2014). Some findings report a positive relationship between general health and this type of inflammation, but these studies often lack clear data (Murray & Saunders 2000). Therefore, dental clinicians and researchers into biological

medicine and dentistry have to address the possible impact that dental inflammation could have on the general health of patients, so that the treatment of asymptomatic apical periodontitis is justified, as this avoids systemic diseases developing or worsening.

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