Endodontic medicine: connections between apical periodontitis and systemic diseases

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Abstract

The prevalence of apical periodontitis (AP) in Europe has been reported to affect 61% of individuals and 14% of teeth, and increase with age. Likewise, the prevalence of root canal treatment (RCT) in Europe is estimated to be around 30–50% of individuals and 2–9% of teeth with radiographic evidence of chronic persistent AP in 30–65% of root filled teeth (RFT). AP is not only a local phenomenon and for some time the medical and dental scientific community have analysed the possible connection between apical periodontitis and systemic health. Endodontic medicine has developed, with increasing numbers of reports describing the association between periapical inflammation and systemic diseases. The results of studies carried out both in animal models and humans are not conclusive, but suggest an association between endodontic variables, that is AP and RCT, and diabetes mellitus (DM), tobacco smoking, coronary heart disease and other systemic diseases. Several studies have reported a higher prevalence of periapical lesions, delayed periapical repair, greater size of osteolytic lesions, greater likelihood of asymptomatic infections and poorer prognosis for RFT in diabetic patients. On the other hand, recent studies have found that a poorer periapical status correlates with higher HbA1c levels and poor glycaemic control in type 2 diabetic patients. However, there is no scientific evidence supporting a causal effect of periapical inflammation on diabetes metabolic control. The possible association between smoking habits and endodontic infection has also been investigated, with controversial results. The aim of this paper was to review the literature on the association between endodontic variables and systemic health (especially DM and smoking habits).

Keywords: diabetes mellitus, immune response, oral health, periapical inflammation, persistent apical periodontitis, root canal treatment, tobacco smoking.

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Introduction
Endodontology includes pulp and periapical biology and pathology. Clinically, however, endodontics is perceived as treatment of the root canal with files and the placement of a root filling, or treatment by surgical endodontics. Whilst the initial diagnoses and the difficulties associated with treatment may be related to the state of the pulp, the ultimate biological aim of this treatment is no longer the preservation of the pulp, but the prevention and elimination of infection in the root canal system to prevent or cure apical periodontitis (AP) (Ørstavik & Pitt Ford 2007).

Apical periodontitis, an inflammatory process around the apex of a root, is primarily a sequel to microbial infection of the pulp space. The infectious aetiology of AP and the main role of microbial factors in the initiation, development and persistence of the condition have been widely documented with the result it can be considered as a disease of bacterial infection (Siqueira & Röças 2014). AP may,
consequently, be viewed as a tissue response to pulp infection from dental caries, trauma, attrition from mastication and abrasion from the use of teeth as tools for survival (Ørstavik & Pitt Ford 2007).

Apical periodontitis is a remarkably prevalent condition (Figdor 2002). In Europe, the prevalence of AP is as high as 34–61% of individuals and 2.8–4.2% of the teeth (Jiménez-Pinzón et al. 2004, López-López et al. 2012a) and increases with age (Eriksen 1998). Root canal treatment (RCT) is the elective treatment for teeth with AP. Nevertheless, complete healing of bone or reduction in the size of apical radiolucencies does not occur in all root filled teeth (RFT). Such cases of nonresolving periapical radioluencies are also referred to as endodontic failures (Nair 2006). Radiolucent periapical lesions (PLs) persist when treatment procedures have not reached a satisfactory standard for the control and elimination of infection. Inadequate aseptic control, poor access cavity design, missed canals, insufficient instrumentation and leaking temporary or permanent restorations are common problems that may lead to persistent AP (Sundqvist & Figdor 1998). In Europe, the prevalence of endodontic treatment is estimated around 41% (Segura-Egea et al. 2004, López-López et al. 2012a). Radiolucent periapical lesions (PLs) persist when treatment procedures have not reached a satisfactory standard for the control and elimination of infection. Inadequate aseptic control, poor access cavity design, missed canals, insufficient instrumentation and leaking temporary or permanent restorations are common problems that may lead to persistent AP (Sundqvist & Figdor 1998). In Europe, the prevalence of endodontic treatment is estimated around 41% (Segura-Egea et al. 2004, López-López et al. 2012a).

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Even though periapical infections cause a number of local tissue responses with the purpose of limiting the spread of the infectious elements, AP may not exclusively be a local phenomenon. The interaction between the lipopolysaccharide (LPS) from anaerobic gram-negative bacteria causing AP with Toll-like receptor 4 (TLR4) on macrophages and neutrophils activates the broad axis of innate immunity, up-regulating pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, TNF-α and prostaglandin E2 (PGE2) (Rôças et al. 2014). These cytokines may be released into the systemic circulation (Doyle et al. 2007) inducing or perpetuating an elevated chronic systemic inflammatory status (Caplan et al. 2006).

Although there is no conclusive scientific evidence indicating that an infected root canal may act as a focus of infection to distant body sites (except for systemically compromised patients), the opposite has not been proven either, that is, there is no clear evidence showing that endodontic infections are an isolated event with no effect on the rest of the body (Siqueira 2011).

It is well known that, in its nonbalanced acute stage, spreading of infection and the inflammatory process to nearby tissue compartments is possible and may bring about severe, but fortunately rare, fatal inflammatory conditions. Moreover, considering the increasing awareness of a potential relationship between persistent, inflammatory disorders of the oral cavity and disease conditions in other organs of the body, acute and chronic manifestations of AP may also be implicated (Marton 2004, Marton & Bergenholtz 2004).

Siqueira & Rôças (2014) cite how primary and post-treatment AP can influence an individual’s overall health and remains a question to be answered in endodontic microbiology. The possible connection between chronic oral inflammatory processes of infectious origin, that is chronic AP and periodontal disease (PD), and systemic health is, nowadays, one of the most interesting aspects faced by the medical and dental scientific community. A question has risen: whether direct cell-to-cell interactions between periodontal or endodontic bacteria and host cells as well as between different human cells or autocrine and paracrine loops of stimulations may influence the function of remote tissues and organs resulting in the pathogenesis or contributing to the pathomechanism of systemic diseases (Marton 2004).

In the two last decades, ‘periodontal medicine’ has developed as a distinct area that focuses on the relationship between PD and systemic diseases (Seymour 2009). Several epidemiological studies have found associations between systemic health and PD. Thus, PD has been associated with diabetes mellitus (DM) (Katz 2001, Soskolne & Klinger 2001), coronary heart disease (CHD) and acute myocardial infarction (AMI) (Beck et al. 1996, Janket et al. 2003, Dörfer et al. 2004, Grau et al. 2004), preterm-low birthweight (Jeffcoat et al. 2003, Marín et al. 2005), respiratory diseases (Scannapieco et al. 2003), osteoporosis in post-menopause women (Bullón et al. 2005), metabolic syndrome (Shrestha et al. 2015) and early loss of memory and capacity for calculation (Noble et al. 2009). The evidence of the association between PD and systemic diseases has focused attention on the diagnosis and treatment of PD, improving, consequently, the patient’s oral and systemic health.

Chronic periodontal and endodontic inflammatory processes have three important similarities (Segura-Egea et al. 2012): 1. Both are chronic infections of the oral cavity; 2. Both are polymicrobial infections sharing a common microbiota with a predominance of Gram-
negative anaerobic bacteria (Siqueira & Rôças 2014); and
3. Elevated cytokine levels may be released systemically from acute and chronic manifestations of both disease processes, for example increased concentrations of inflammatory mediators have been detected both in the gingival crevicular fluid of subjects with PD and in the periapical tissues of endodontically involved teeth (Caplan 2004, Caplan et al. 2006).

Likewise, one might assume that AP is associated with the same systemic disorders that are associated with PD (JOE Editorial Board 2008, Segura-Egea et al. 2012). Therefore, ‘endodontic medicine’ should be developed following the same path as ‘periodontal medicine’: evaluating the association between endodontic and systemic diseases. However, the influence that chronic periapical processes could produce on highly prevalent systemic diseases, such as diabetes and CHD has been poorly studied. The lack of scientific studies on this topic might be masking the potential risk of retaining teeth with chronic AP and the real importance and health advantages of endodontic treatments to patients, doctors and dentists (Segura-Egea et al. 2012).

On the other hand, the impact of systemic diseases and some general habits, such as smoking, on pulp and periapical health also needs to be further investigated (Walter et al. 2012a). Strindberg (1956), in his classic study, did not find the general health status of the patient as a significant factor affecting periapical health. However, Marending et al. (2005) reported that the integrity of the nonspecific immune system was a significant predictor for endodontic initial treatment and retreatment outcome \( (P = 0.05) \). Ng et al. (2008) also demonstrated the impact that an impaired nonspecific immune system had on the healing of periapical tissues. Thus, pro-inflammatory status and impaired immune response associated with systemic diseases can affect the reparative response of the dental pulp and periapical healing, influencing the two main endodontic variables: the prevalence of AP and the frequency of RCT.

**Association between endodontics and diabetes mellitus**

Diabetes mellitus is a clinically and genetically heterogeneous group of disorders affecting the metabolism of carbohydrates, lipids and proteins, in which hyperglycaemia is a main feature (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2000). These disorders are due to a deficiency in insulin secretion caused by pancreatic β-cell dysfunction and/or insulin resistance in liver and muscle (Mealey & Oates 2006). Diabetes affects more than 9% of the adult population, and its high morbidity and mortality amongst affected individuals has a substantial impact on national healthcare systems (Mealey & Oates 2006). Aged-adjusted and country-adjusted prevalence of Type 2 diabetes mellitus (T2DM) in 11 European countries in 2004 was 10.2% in men and 8.5% in women (Espelt et al. 2013).

Glycated haemoglobin (HbA1c) has been used as a ‘gold standard’ for mean glycaemia and as a measure of risk for the development of DM complications (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2000). The American Association of Clinical Endocrinologists (AACE) considers HbA1c levels ≤6.5% as a goal for optimal glycaemic control in diabetic patients (Gionfriddo et al. 2014).

Type 1 diabetes results from cellular-mediated autoimmune destruction of pancreatic β-cells, which usually leads to total loss of insulin secretion; in contrast, type 2 diabetes is caused by resistance to insulin combined with a failure to produce enough additional insulin to compensate for the resistance (Mealey & Oates 2006). T2DM is characterized by hyperglycaemia in the context of insulin resistance and β-cell dysfunction (Montane et al. 2014). The aetiology of T2DM is multifactorial, involving a complex interplay between genetic, epigenetic and environmental factors (Jiang et al. 2013). T2DM is frequently linked to obesity, which contributes to insulin resistance through elevation of circulating levels of free fatty acids, derived from the adipocytes, which inhibit glucose uptake, glycogen synthesis and glycolysis (Oakes et al. 1997). However, in one-third of obese individuals, β-cell mass is reduced by a marked increase in β-cell apoptosis, which results in inadequate production of insulin (Tunes et al. 2010). Many studies have shown that inflammation plays a very important role in the pathogenesis of T2DM. Inflammatory mechanisms and cytokine production activated by stress via the inflammasome may further alter the normal structure of β-cells by inducing pancreatic islet cell apoptosis (Montane et al. 2014).

**Diabetes mellitus and oral health**

Diabetes mellitus induces changes to immune cell function, up-regulating pro-inflammatory cytokines
from monocytes/polymorphonuclear leucocytes and down-regulating growth factors from macrophages, predisposing to chronic inflammation, progressive tissue breakdown and diminished tissue repair capacity (Iacopino 2001). This immune phenotype leads to the oral complications of DM, including xerostomia, delayed wound healing of oral mucosa, candidiasis, increased incidence and severity of caries, pulp-periapical infections, PD and dry mouth syndrome (Little et al. 1997). Moreover, evidence has consistently indicated that DM is a risk factor for increased severity of PD, both gingivitis and periodontitis (Salvi et al. 2008). One of the chronic complications of DM, microangiopathy, would lead to decreased blood flow and thus the input of nutrients and oxygen to the periodontal tissues, facilitating progression of PD, loss of support, increasing periodontal pockets, mobility and a poorer response to periodontal treatment (Thomson et al. 2004). Poor control of DM and hyperglycaemia will further diminish the immune response, with decreased leucocyte function and delay of wound healing, and are associated with aggressive forms of PD (Delamaire et al. 1997, Iacopino 2001, Salvi et al. 2008).

Conversely, PD may be a risk factor for worsening glycaemic control amongst patients with diabetes and may increase the risk of diabetic complications (Katz 2001). PD may initiate or propagate insulin resistance in a manner similar to that of obesity, by enhancing activation of the overall systemic immune response initiated by cytokines (Mealey & Oates 2006, Allen et al. 2009). The destruction of the alveolar bone and periodontal ligament, leads to a pathogenic and inflammatory reactions that continues to systemic level, due to the large amount of surface epithelium of the periodontal pockets that allows, through three possible mechanisms, the passage of bacteria and their products to the body (Mealey & Koekkevold 2004):

1. **Bacteraemia**: microorganisms enter the bloodstream, aren’t removed and spread;  
2. **Metastatic damage**: caused by endotoxin release and LPSs which are lethal to cells; and  
3. **Metastatic inflammation**: caused by antigen-antibody reactions and release of chemical mediators.

The continuous passage of bacterial LPS of gram-negative bacteria from biofilms, and proinflammatory cytokines into the bloodstream, would be the basis of the influence of the PD at the level of general health and susceptibility to certain diseases. Furthermore, in the case of DM, the PD becomes a risk factor for the synthesis of advanced glycation end products (AGEs), that bind to membrane receptors on phagocytic cells and overregulate the functions of pro-inflammatory chemical mediators that maintain a chronic hyperglycaemia, as occurs in diabetes (Saremi et al. 2005). In fact, some studies describe the improvement of diabetes with the treatment of PD, with decreased serum levels of TNF-alpha, fibrinogen, HbA1c, and hs-CRP (C-reactive protein of high sensitivity) (Katagiri et al. 2009, Correa et al. 2010). However, the literature is insufficient and inconclusive to clearly support periodontal treatment as a means to improve serum HbA1c levels in patients with DM (Mauri-Obradors et al. 2014).

**Diabetes mellitus and apical periodontitis: animal studies**

As far as studies in animal models are concerned, Kohsaka et al. (1996) studied histologically and histometrically changes in pulpal and periapical tissues after pulpal exposure in streptozotocin-induced diabetic rats. In experimental rats, inflammation in the apical periodontal ligament and root resorption and alveolar bone resorption were more severe than in control rats. Diabetic rats had larger PLs. Fouad et al. (2002) induced PLs in first molars of female nonobese diabetic (NOD) mice by inoculating a mixture of aerobic and facultative anaerobic bacteria. Then, they measured periapical lesion size histomorphometrically, observing more pronounced periapical inflammation and larger PLs in diabetic rats compared with controls. Iwama et al. (2003) studied the development of periradicular lesions 4 weeks after exposure of the pulp in GK rats with spontaneous noninsulin-dependent DM and control Wistar rats. Histologic analysis demonstrated that hyperglycaemic diabetic rats had greater bone resorption and larger periradicular lesions than control rats. Garber et al. (2009) studied the effect of hyperglycaemia on pulp healing in exposed rat pulps capped with mineral trioxide aggregate. They found an inverse association between dentine bridge formation and inflammatory cell infiltration: dentine bridge formation was inhibited in diabetic rats and more inflammation was observed in these pulps. Bain et al. (2009) described the development of insulin resistance in pregnant rats with induced periapical abscesses. Endodontically affected pregnant rats had increased interleukins and serum TNFα levels, together with significant increases in blood glucose and serum insulin concentrations.
Kodama et al. (2011) conducted an experimental study to determine whether diabetes induces or enhances PD or dental caries and AP. They used a strain of rat that develops spontaneous diabetes after 10 months of age. Their results revealed that the incidence and severity of both molar caries and alveolar bone resorption were much higher in rats with chronic diabetes. Liu et al. (2012) reported that metformin, one of the antihyperglycaemic agents commonly used for the treatment of type 2 diabetes, decreases periapical bone loss area after pulp exposure in Wistar rats through lowering the RANKL/osteoprotegerin (OPG) ratio, reducing the number of osteoclasts and bone resorption areas. Wolle et al. (2013) evaluated the development of PLs in a rat model of type 2 diabetes and assessed the potential actions of the antioxidant agent tempol. Neither radiographic nor histologic analysis revealed any significant difference between controls and type 2 diabetic rats. In diabetic rats, AP was refractory to tempol treatment.

Recently, Astolphi et al. (2013) evaluated the effect of PLs on insulin signalling and insulin sensitivity in rats, reporting that PLs caused alterations to both insulin signalling and insulin sensitivity, with insulin resistance, probably because of elevation of plasmatic TNFα. The same group carried out an experimental study on Wistar rats using the model of streptozocin-induced diabetes. AP was induced by pulp exposure to the oral environment and PD was induced by periodontal ligature. Cintra & da Silva Facundo (2013) reported changes in the lipid profile in diabetic rats with pulpitis, concluding that the presence of oral infections and diabetes is associated to changes in tryglyceride levels in diabetic rats. In another report Cintra et al. (2014a) investigated AP and PD for their effects on both blood glucose concentrations and glycylated haemoglobin levels (HbA1c). Results showed that inflammatory infiltrate and alveolar bone resorption were more severe in diabetic rats. They concluded that oral infections affect glycaemic conditions in diabetic rats and increase HbA1c levels in normoglycaemic and diabetic rats. In a third paper, Cintra et al. (2014b) reported that the combination of AP and PD increased serum IL-17 levels in DM and normoglycaemic rats, and increased neutrophil levels in DM rats. They found that diabetes increased neutrophil levels and bone resorption in rats. Interleukin-17 (IL-17) is a proinflammatory cytokine that mediates multiple chronic inflammatory responses, including angiogenesis, recruitment of inflammatory cells, and induction of proinflammatory mediators by endothelial and epithelial tissues (Ouyang et al. 2008, Queiroz-Junior et al. 2010). In the more recent report (Cintra & da Silva Facundo 2014c), the authors investigated the relationship between blood profile and histologic findings in both AP and PD associated with diabetes in Wistar rats. They concluded that diabetes accelerated the development and progression of AP and PD and caused an increase in average erythrocyte volume as well as leucocyte and neutrophil counts. Both oral infections increase the total number of leucocytes, the number of neutrophils and lymphocytes, and blood glucose concentrations in DM rats.

**Diabetes mellitus and endodontics: human studies**

Several clinical and epidemiological studies carried out in humans have analysed the association between endodontic variables and DM. The main endodontic variables analysed in these studies are as follows:

1. The prevalence of AP;
2. The prevalence of RCT; and
3. The outcome of RCT, assessed as the percentage of RFT with or without PLs, or as the prevalence of tooth extraction after nonsurgical RCT (NSRCT).

In diabetic patients, the variables usually assessed are blood glucose and glycated haemoglobin levels.

**Diabetes mellitus and the prevalence of apical periodontitis**

Is there an association between the prevalence of AP and DM? The first human studies (Bender et al. 1963) highlighted the substantial proportion of diabetics amongst patients with odontogenic infections. Bender & Bender (2003) found a high rate of asymptomatic tooth infections in diabetics exhibiting poor glycaemia levels of an unclear cause concluding that ‘clinical and radiographic studies by other investigators have shown that there is a greater prevalence of PLs in diabetics than in nondiabetics’. Certainly, numerous epidemiological studies have compared the prevalence of AP in diabetic and nondiabetic patients. Thus, Falk et al. (1989) carried out a clinical and radiographic study analysing the prevalence of PLs in type 1 diabetic patients. They recorded the number of teeth, carious lesions, RFT and PLs in ninety-four long duration diabetics, 86 short duration diabetics and 86 nondiabetic patients. There were no significant differences between long and short duration diabetics and nondiabetics in the mean number of teeth with PLs, but, amongst the diabetics, there was a group of
individuals who had more PLs than controls, and the extension of PLs was greater in long duration diabetics. Ueta et al. (1993) focused their study in the prevalence of DM mellitus in patients with odontogenic infections, finding a disproportionately high percentage of severe clinical infections, both pulp-periapical and periodontal, in diabetic patients. Amongst 21 severe odontogenic infections, DM was detected in five cases, concluding that diabetes is a predisposing condition for odontogenic infections. Britto et al. (2003) studied the prevalence of PLs in patients with and without diabetes, finding one or more teeth with AP in 97% and 87% of diabetic patients and control subjects, respectively, concluding that there was no significant association between AP and diabetes. On the contrary, in a cross-sectional study carried out by Segura-Egea et al. (2005), the prevalence of AP was determined using periapical radiographs and the periapical index (PAI) (Orstavik et al. 1986), in patients with and without type 2 DM. Results demonstrated that AP in one or more teeth was significantly more frequent in diabetic patients (81%) compared to healthy control patients (58%) (OR = 3.2; P < 0.05); moreover, the percentage of teeth with AP was significantly higher in diabetics (7%) compared to controls (4%) (OR = 1.8; P < 0.01). In another cross-sectional study carried out by the same group in Spain (López-López et al. 2011), this time including only well-controlled diabetic patients as assessed by glycated haemoglobin levels, the results revealed that the frequency of radiographic signs of AP in at least one tooth was significantly higher in diabetic patients (74%) compared to controls (42%). Multivariate logistic regression analysis concluded that the likelihood of having AP was almost four times higher in diabetic patients compared to nondiabetic subjects (OR = 3.9; P < 0.01). Another cross-sectional study carried out in an adult Brazilian population (Marotta et al. 2012) using full-mouth radiographs and Strindberg’s criteria for the diagnostic of AP (Strindberg 1956), also found that AP was significantly more common in teeth from diabetic individuals (15%) than in nondiabetic controls (12%) (P = 0.05). The significance was mostly because of the prevalence of AP in untreated teeth: the frequency of AP lesions in untreated teeth was significantly higher in the teeth from type 2 diabetics (10%) compared to (7%) (P = 0.03).

The results of studies conducted so far are inconclusive, but suggest an association between DM and a higher prevalence of AP, odontogenic infections and greater size of PLs. Longitudinal studies are needed to further investigate this topic.

**Diabetes mellitus and the prevalence of root canal treatment**

The second question is whether there is an association between the prevalence of RCT, and DM. Falk et al. (1989) found no significant differences between long and short duration diabetics and nondiabetics in the mean number of RFT. Women with long diabetes duration, however, exhibited more RFT with PLs than women with short diabetes duration and women without diabetes. In the cross-sectional study carried out by Segura-Egea et al. (2005) in a sample of the Spanish population, no significant association between diabetes and prevalence of RFT was found (OR = 0.56; P = 0.25). The same percentage of RFT (2%) was found both in diabetic and control subjects. Marotta et al. (2012) also found no association between well-controlled diabetic status and the prevalence of RFT (P = 0.25). However, in another cross-sectional study also carried out in Spain (López-López et al. 2011) comparing the endodontic status of well-controlled diabetic patients (HbA1c = 6.6 ± 0.6) and control subject without DM, the percentage of subjects with at least one root filled tooth (RFT) was significantly higher in diabetics (70%) compared to controls (50%). Multivariate logistic regression analysis concluded that the likelihood of having at least one RFT was twice in diabetic patients compared to nondiabetic subjects (OR = 2.3; P < 0.05). It can also be concluded that there is inconclusive evidence about the association of diabetes with a higher prevalence of RCT.

**Diabetes mellitus and the outcome of root canal treatment**

The third question to be formulated is whether there is an association between DM and the outcome of RCT. This possible relationship can be investigated by analysing two variables: the prevalence of RFT with AP and the prevalence of tooth extraction after NSRCT.

In relation to the prevalence of RFT with AP, Falk et al. (1989) found a higher frequency of RFT with PLs in long duration diabetics compared to non-diabetic patients. Fouad & Burleson (2003) investigated endodontic treatment outcome data in 140 patients, 73 with DM, finding that patients with diabetes had a reduced likelihood of success (assessed clinically and radiographically) following RCT in cases with preoperative periradicular lesions and increased flare-ups.
during treatment. In a retrospective cohort study (Britto et al. 2003), using a full-mouth series of periapical radiographs and panoramic radiographs and assessing the periapical status with the Strindberg’s criteria (Strindberg 1956), no significant difference between controls (44.2%) and diabetics (46.4%) in the percentage of RFT with AP (P > 0.05) was found. However, men with type 2 DM who had RFT were more likely to have residual lesions. Similar results were found in two studies comparing well-controlled diabetic patients and control subjects, one using panoramic digital radiographs (López-López et al. 2011) and the other using full-mouth periapical radiographs and panoramic radiographs (Marotta et al. 2012), which found 24% and 38% of RFT with radiolucent PLs in the control group, respectively, and 46% of RFT with AP in the diabetic group (P > 0.05). In the study of Segura-Egea et al. (2005), carried out using periapical radiographs and without taking into account the metabolic control of diabetic patients, 83% of RFT had radiographic signs of AP in the diabetic group, whereas only 69% had PLs in the control group; however, these differences were not significant (OR = 3.3; P > 0.05). Recently, Ferreira et al. (2014) compared the success rate of RFT, assessed radiographically and clinically, in two groups of 23 patients, one healthy controls and the other diabetics, and found no significant differences between the groups when using the PAI (P > 0.05).

Although it could be concluded that there is no evidence indicating that diabetes is associated with a higher prevalence of RFT with AP, when all the data of these six epidemiological studies analysing this topic are pooled (including 1076 RFT), the result became statistically significant (Table 1; OR = 1.7; CI 95% = 1.3–2.2; P = 0.0003).

On the other hand, it must be taken into account that some of the periapical radiolucencies associated with RFT and identified as AP in the cited epidemiological studies, probably represent healing lesions, particularly if the time elapsed since treatment was <2 years (Dugas et al. 2003). Indeed, this is a recognized limitation of cross-sectional studies (Jiménez-Pinzón et al. 2004).

To evaluate the association between the prevalence of RFT extraction and DM, Mindiola et al. (2006) carried out an epidemiological study on a regional population of Native Americans, identifying factors affecting the retention of RFT. The results suggested that diabetes contributed to decreased retention of RFT (P < 0.01). Doyle et al. (2007), in a retrospective study analysing 196 root filled treated teeth, evaluated whether DM was associated with the outcome of patients undergoing NSRCT. Results showed that the treatments undertaken in diabetics were more likely to fail, revealing a borderline significant association (P = 0.063) between DM and RFT extraction. Another epidemiological study carried out by Wang et al. (2011) analysing 49 334 RFT, 4358 in diabetic patients, found that DM was a significant risk factor for tooth extraction after RCT (OR = 1.8; P < 0.01), concluding that DM contributes to decreased retention of RFT. Ng et al. (2011) carried out a prospective study involving 1600 RFT. The multiple Cox regression model concluded that diabetic patients were associated with threefold more RFT loss than healthy counterparts (Hazard ratio = 3.2–3.4; P < 0.01). In conclusion, there is scientific evidence to demonstrate a poorer prognosis for RFT in diabetics. Thus, diabetic patients have delayed periapical repair and greater likelihood of RFT loss.

### Metabolic control of diabetes mellitus and apical periodontitis

Finally, only a few studies have analysed the relationship between metabolic control of DM and endodontic variables. In a pioneer study, Bender et al. (1963) argued that the lack of control in DM could delay healing of PLs and increase their size, despite having received endodontic treatment. On the contrary, in well-controlled diabetic patients PLs healed as readily as in nondiabetics. Cheraskin & Ringsdorf (1968) studied the radiographic healing of periradicular periodontitis (AP) in diabetic patients and control subjects: summary of studies and pooled data

<table>
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<tr>
<th>Authors (year)</th>
<th>Total RFT (%)</th>
<th>Diabetics Total RFT (%)</th>
<th>Controls Total RFT (%)</th>
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lesions after RCT in 12 patients with low-plasma glucose and 13 patients with high-plasma glucose, finding a lower reduction of the PLs in patients with high glucose levels (48% reduction) compared to low glucose group (74% reduction). Recently, Sánchez-Domínguez et al. (2015) carried out a cross-sectional study on 83 diabetic patients using orthopantomographs and PAI. They assessed the metabolic control of DM measuring glycated haemoglobin levels and classifying diabetic patients as well-controlled (HbA1c < 6.5%) or poor-controlled (HbA1c > 6.5%). Results revealed that periapical status correlated significantly with glycated haemoglobin levels. Multivariate logistic regression analysis demonstrated a significant association between periapical status of RFT and HbA1c levels ($P < 0.05$).

Overall, the results are inconclusive, although some studies suggest that chronic periapical disease may contribute to diabetic metabolic dyscontrol. Once more, further prospective studies are needed.

**Biological mechanisms linking periapical status and diabetes mellitus**

To validate a relationship between diabetes and AP, biologically plausible mechanisms must be evident to explain the pathobiology of the interactions. In diabetics, there are three main alterations: impaired innate immunity, hyperglycaemia and the formation of irreversibly glycated-proteins forming AGEs (Fig. 1). Innate immunity is the first line of defence against pathogens. In DM the function of innate immunity cells is altered. Neutrophil phagocytosis is decreases and macrophages are up-regulated, with increased production of pro-inflammatory cytokines (Lima et al. 2013). However, high glucose levels can inhibit...

![Figure 1](image-url) Biological mechanisms by which diabetes mellitus (DM) can influence periapical status. There are three main biological mechanisms in DM (DM): impaired innate immunity, hyperglycaemia and the formation of irreversibly glycated-proteins forming advanced glycation end products (AGEs). The function of innate immunity cells is altered; neutrophil phagocytosis is decreased, and macrophages are up-regulated, with increased production of pro-inflammatory cytokines. On the other hand, the advanced glycated end products that hyperglycaemia provokes, bind to collagen leading to alterations in bone metabolism, reducing bone formation and osteoblastic differentiation. Moreover, AGEs interact with specific receptors in macrophages activating NF-$\kappa$B, increasing cellular oxidant stress and up-regulating pro-inflammatory cytokines. Finally, the hyperglycaemic status provokes apoptosis of osteoblasts and fibroblasts, inhibition of collagen production and inhibition of osteoblastic cell proliferation and differentiation. Thus, as a result DM predisposes to chronic inflammation, diminishes tissue repair capacity, and causes a greater susceptibility to infections and delays wound healing. In inflamed periapical tissues of root filled teeth (RFT), DM compromises the immune response aggravating periapical chronic inflammation and impairing bone turnover and wound healing, increasing the prevalence of persistent apical periodontitis.
macrophone function resulting in an inflammatory state that impairs host cellular proliferation, delaying wound healing of dental pulp and periapical tissues (Garber et al. 2009).

Secondly, it has been stated that hyperglycaemia causes structural alterations in dental pulp and periapical tissues by impairing collateral circulation (Bender & Bender 2003, Lima et al. 2013). Moreover, a reduction in IL-4 and OPG (Duarte et al. 2012) and an up-regulation in IL-1b, IL-6, IL-8, IL-10, TNF-α and receptor activator of nuclear factor kappa B ligand (RANKL) (Lima et al. 2013, García-Hernández et al. 2012) in the inflammatory response in hyperglycaemic conditions has been described. Additionally, hyperglycaemia up-regulates the activity of differentiated osteoclast cells, and it has been proposed that could increase bone resorption (Dienelt & zur Nieden 2011).

A third possible mechanism linking DM and periapical status could be AGEs. AGEs are synthesized via the nonenzymatic glycation and oxidation of proteins, lipids and nucleic acids during chronic hyperglycaemia. AGEs interact with specific receptors in macrophages (RAGE) activating nuclear factor-kappa beta (NF-κβ), increasing cellular oxidant stress and up-regulating pro-inflammatory cytokines (Cai et al. 2012). The formation of irreversible AGEs in DM compromises the tissues and alters the constitution of the extracellular matrix (ECM) components. As periapical tissues contain ECM targeted by AGE, DM could have severe implications in subjects with AP (Gurav 2013). AGEs bind to collagen leading to alterations in bone metabolism, reducing bone formation and osteoblastic cell proliferation and differentiation (Tanaka et al. 2013). A linear correlation between the expression of RAGE and NF-κβ has been demonstrated in human inflamed periradicular tissues (Crabtree et al. 2008). The co-expression of RAGE and AGE by endothelial cells in human periapical granulomas has been demonstrated, suggesting that the engagement of RAGE and AGE may trigger cellular activation mediating periapical tissue injury (Takeichi et al. 2011). Recently, it has been reported that AGEs bind to its receptor in periodontal ligament fibroblasts provoking apoptosis and inhibition of collagen production (Li et al. 2014). Therefore, AGEs could impair periapical repair after RCT.

Thus, as a result, diabetes predisposes to chronic inflammation, diminishes tissue repair capacity, causes a greater susceptibility to infections and delayed wound healing. In inflamed periapical tissues of RFT, DM can compromise immune response aggravating periapical inflammation and impairing bone turnover and wound healing, increasing the prevalence of persistent AP.

On the other hand, the mechanisms by which periapical status could affect the glycaemic control in diabetic patients (Fig. 2) can be hypothesised. Type 2 diabetes is a manifestation of the host’s inflammatory response, because an ongoing cytokine-induced acute-phase response (a low-grade inflammation that occurs through activation of the innate immune system) is closely involved in the pathogenesis of this disease (Santos Tunes et al. 2010). Similarly, the mechanisms of the host-mediated response in AP involve activation of the broad axis of innate immunity, specifically by up-regulation of pro-inflammatory cytokines from monocytes and polymorphonuclear leucocytes. Therefore, periapical chronic inflammation could induce or perpetuate an elevated chronic systemic inflammatory status, contributing to increased insulin resistance and poor glycaemic control (Montoya-Carralero et al. 2010, Segura-Egea et al. 2012). The action of inflammatory mediators released in periapical inflammation could be associated with the development of insulin resistance, which is influenced by genetically modified environmental factors, including decreased physical activity, poor nutrition, obesity and infection (Pickup 2004, Segura-Egea et al. 2012, 2013, 2014). The LPS from anaerobic gram-negative bacteria causing AP binds to their specific receptors in immune cells (TLRs) and activates intracellular pathways, specifically the NF-κβ on macrophages up-regulating pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, tumour necrosis factor alpha (TNF-α) and PGE2, contributing to the pro-inflammatory systemic status of diabetics (Pickup 2004, Segura-Egea et al. 2014). These locally produced cytokines move into the systemic circulation (Doyle et al. 2007), where they can interact with the free fatty acids and AGEs, characteristic of type 2 DM (Cai et al. 2012). The activation of these inflammatory pathways in immune cells (monocytes or macrophages), endothelium cells, adipocytes, hepatocytes and muscle cells enhances the activation of the overall systemic immune response initiated by cytokines (Mealey & Oates 2006, Allen et al. 2009) and could promote an increase in the overall insulin resistance, altering the metabolic control in patients with both DM and chronic AP (Segura-Egea et al. 2012, Hu et al. 2015). Recently, it has been reported that, under diabetic pulp conditions, AGEs increase mRNA expression of IL-1β in dental pulp cells.
through the RAGE-MAPK signalling pathway (Nakajima et al. 2015).

**Conclusion**

The results of the studies conducted so far are not conclusive, but suggest an association between DM and AP. There is evidence associating DM with a higher prevalence of AP, greater size of periapical osteolytic lesions, greater likelihood of asymptomatic periapical infections and delay/arrest of periapical repair. The prognosis for RFT is worse in diabetics, with a higher rate of RCT failure with increased prevalence of persistent chronic AP. On the other hand, there are data suggesting that chronic periapical disease may contribute to diabetic metabolic dyscontrol. However, prospective epidemiological studies are needed to better understand the relationship between DM and periapical inflammation. As diabetes is the third most prevalent condition in medically compromised patients seeking dental treatment (Dhanuthai et al. 2009), dentists should be aware of the possible relationship between endodontic infections and DM and take it into account when treating patients.

**Association between endodontics and smoking habits**

Tobacco consumption is a global pandemic, widespread in Europe, killing half of all lifetime users. In 2011, six million people died as a result of tobacco use, and by the year 2030 eight million people are expected to die annually (Eriksen et al. 2012). According to the WHO study Health Behaviour in School-aged Children (HBSC), approximately 18% of 15-year-old adolescents smoke cigarettes at least once a week (Currie et al. 2012). A recent study carried out in Sweden has found that smoking prevalence increased from 3% amongst 12–13 year olds to 25%
amongst 17–18 year olds (Joffer et al. 2014). Amongst all adults, this percentage is around 27% (Wlodarczyk et al. 2013). In Europe, tobacco smoking causes approximately 1.6 million premature deaths and 13 million Europeans currently suffer from tobacco related diseases (Zatoriski et al. 2012). Amongst the elderly, the overall smoking prevalence in 17 European countries was 11.5%, with smoking habits being of a higher prevalence in eastern/central Europe for men (20.3%) and in northern Europe for women (13.1%) (Lugo et al. 2013).

Smoking habits and oral health

It is already known that tobacco use is a well-established risk factor for systemic and oral health (Warnekulasuriya et al. 2010, Hutunnen et al. 2011, Walter et al. 2012a). The results of several studies suggest that smoking increases the risk of caries (Sgan-Cohen et al. 2000, Fure 2004), and cigarette smoking, even passive smoking, has been identified as a strong environmental risk factor for PDs (Warnekulasuriya et al. 2010, Walter et al. 2012b). The harmful effects of tobacco smoking on periodontal bone have been demonstrated in several cross-sectional and longitudinal studies (Krall et al. 1999, Bergström et al. 2000). Smokers have a diminished response to periodontal therapy and have approximately half as much improvement in probing depths and clinical attachment levels following nonsurgical and various surgical modalities of therapy (Johnson & Hill 2004).

Smoking has major effects on the host response to infections and has a long-term chronic effect on many important aspects of the inflammatory and both cell-mediated immunity and humoral immunity (Palmer et al. 2005). Smoking induces a significant systemic neutrophilia and protease release from neutrophils, and suppression of neutrophil cell spreading, chemokinesis, chemotaxis and phagocytosis (Palmer et al. 2005, Ryder 2007). Research on gingival crevicular fluid has demonstrated that there are lower levels of cytokines, enzymes and possibly polymorphonuclear cells in smokers (Palmer et al. 2005).

Smoking habits and apical periodontitis

On this basis, it can be assumed that smoking might be a risk factor for AP, exerting a negative influence on the apical periodontium of endodontically compromised teeth, facilitating the extension of the process of periapical bone destruction and/or interfering with healing and repair events following endodontic treatment. Consequently, an increased number and/or size of PLs would be expected in smokers. The literature demonstrates conflicting evidence relating smoking with endodontic disease and prognosis, as well as to whether smoking increases the prevalence of AP (Duncan & Pitt Ford 2006).

Studies finding no association between smoking and endodontic variables

Amongst the investigations carried out to study the relation between smoking and AP, those finding no association between tobacco smoking and AP will be discussed first. Bergström et al. (2004) analysed AP in terms of radiographically detectable and measurable destructive changes of periapical bone. Using periapical radiographs, they compared the prevalence of PLs in 81 smokers, 63 former smokers and 103 nonsmokers, finding that 56%, 57% and 46%, respectively, had at least one tooth with AP, concluding that smoking was not significantly associated with apical AP ($P > 0.05$). The prevalence of RFT was also investigated, with 45% of nonsmokers having at least one RFT, compared to 68% of smokers and 67% of former smokers ($P > 0.05$). Finally, the prevalence of RFT with radiolucent PLs was also determined, with no association detected between periapical status of RFT and smoking habits ($P > 0.05$).

Marending et al. (2005) analysed the influence of smoking on RCT outcome. They carried out a follow-up study including 66 patients who had undergone RCT, followed 46 ± 12 months, and using the PAI (Orstavik et al. 1986) to assess periapical status. No association between smoking and periapical status of RFT was found ($OR = 0.80; P = 0.85$). Frisk & Hakeberg (2006), in a cross-sectional study including 981 women, 191 smokers and 653 nonsmokers, and using orthopantomograms to assess periapical status, also found no significant association between AP and smoking ($OR = 1.35; P > 0.05$). Touré et al. (2011) analysed the factors related to extraction of 119 RFT, finding no significant differences between smokers and nonsmokers. In another cross-sectional study, Rodriguez et al. (2013) also found no significant relationship between smoking habits and AP. Using periapical radiographs and the PAI score system (Orstavik et al. 1986), they evaluated the periapical status of 66 smokers, 28 former smokers and 67 nonsmokers, concluding that smoking status did not predict AP.
Studies finding association between smoking and endodontic variables

Although five epidemiological studies have found no significant association between tobacco smoking and endodontic variables, there are nine studies whose results suggest that this association exists. Aleksejuniene et al. (2000), in a cross-sectional study, were the first to identify smoking as a risk indicator for AP in an adult Lithuanian population. In a cross-sectional study, they analysed radiographically, using orthopantomograms and the PAI score system (Ørstavik et al. 1986), the periapical status of 147 patients, concluding that smoking and AP were significantly associated (P < 0.05). Kirkevang & Wenzel (2003) published a cross-sectional study, carried out on 613 patients and using periapical radiographs and the PAI system (Ørstavik et al. 1986), reported that smoking was associated statistically with AP (OR = 1.64; P = 0.05). Krall et al. (2006) carried out a longitudinal study with 2–28 years follow-up, including 811 dentate male participants. Radiographic evaluation demonstrated a dose response relationship between cigarette smoking and the frequency of RCT. The risk amongst cigarette smokers increased with greater number of years of exposure and decreased with length of abstinence. Compared with never smokers, current cigarette smokers were 1.7 times as likely to have RFT (P < 0.001). In a retrospective study (Doyle et al. 2007), assessed clinically and radiographically the outcome of 196 nonsurgically treated RFT, and reported that RCT in smokers had fewer successes and more failures than in nonsmoker patients (P < 0.05). The same year, Kirkevang et al. (2007) analysed individual and tooth specific factors associated with the incidence or the persistence of AP in a general population, concluding that smoking was a significant risk factor when assessed separately (OR = 1.9; P < 0.05). Ojima et al. (2013) studied the characteristics of dental care of 2835 current smokers and 6850 nonsmokers finding that caries/endodontic treatment were significantly more frequent in smokers compared to nonsmokers (47.1% vs. 43.6%, P = 0.002).

The group at the University of Sevilla has carried out three epidemiological studies. First, they carried out a cross-sectional study (Segura-Egea et al. 2008) analysing periapical radiographs and using the PAI score system (Ørstavik et al. 1986) to determine the prevalence of radiographic periapical radiolucencies in 71 nonsmokers and 109 smokers. This study supported the concept that smoking is associated with an increase in the prevalence of AP, being a risk factor for AP (OR = 4.2; P < 0.01) and enhancing the occurrence of RCT (OR = 2.0; P < 0.05). In the multivariate logistic regression analysis, with AP as dependent variable and adjusting for age, gender, number of teeth and endodontic status, smoking remained significantly associated with periapical status (OR = 4.4: P < 0.01). However, there was no association between smoking and the prevalence of RFT with AP (P > 0.05). In another cross-sectional study (Segura-Egea et al. 2011), carried out in a sample of 100 hypertensive subjects, 50 smokers and 50 nonsmokers, the percentages of patients with AP in one or more teeth or with at least one RFT were significantly higher amongst smokers (P < 0.05). Finally, in a case–control study (López-López et al. 2012b) including 79 smoker and 79 nonsmokers, age- and sex-matched, tobacco smoking was strongly associated with the presence of radiographically diagnosed PLs. Amongst the smokers, 75% had a history of smoking, whereas in the control group only 13% had been smokers (OR = 20.4: P = 0.0000). After multivariate logistic regression analysis adjusting for covariates (age, gender, number of teeth, RFT, RFT with a technically unsatisfactory root filling and diabetes), a strong association was observed between the presence of at least one radiographically detectable periapical lesion and history of smoking (OR = 32.4: P = 0.0000), concluding that smoking significantly predicts AP.

Biological mechanisms linking periapical status and smoking

Although the effects of smoking on the wound healing process are well recognized in clinical dental practice (Scabbia et al. 2001), the particular mechanisms implicated are not well known. However, several biological mechanisms that could explain, at least in part, the relationship between endodontic variables and tobacco smoking can be suggested (Fig. 3). First, smoking affects the microvasculature, both the morphological and functional aspects of the microcirculation, decreasing the oxygen supply to the blood and causing endothelial cell injury because of free radicals (Lehr 2000, Freiman et al. 2004). It can be hypothesized that inflamed periapical tissues in smokers could experience restrictions in nutrients and oxygen supply.

Secondly, tobacco smoking has been shown to cause delay fibroblast migration to the wound area...
(Wong et al. 2004) and fibroblast dysfunction, with altered collagen synthesis and impaired tissue repair (Raulin et al. 1988). Smokers have an increased RANKL/osteoprotegerin ratio in saliva and in serum, mainly because of decreased levels of osteoprotegerin (Johannsen et al. 2014), with bone loss exacerbation (Lindquist et al. 1996).


Fourthly, smoking induces a stronger systemic inflammatory response, increasing C-reactive protein levels in serum and the release of potentially tissue-destructive substances such as reactive oxygen species, collagenase, serine proteases and the pro-inflammatory cytokines IL-1β and TNFα (Barbieri et al. 2011, Johannsen et al. 2014).

Finally, a local and direct pro-inflammatory effect of smoking on periapical tissues has been demonstrated. In periapical granulomas removed from 46 patients, the endogenous synthesis of eicosanoids and isoprostanes, the conversion rate of (14)C labelled arachidonic acid and lipooxygenases (LOX) products was analysed. Results demonstrate that in smokers with granuloma due to AP, the products of lipid peroxidation as 8-iso-PGF(2α) and products of the LOX-pathway were increased at the expense of cyclooxygenase products (Eder et al. 2012). Any one of these pathophysiologic pathways can potentially affect the health of the tooth pulp and periradicular bone, resulting in a higher frequency of radiographic PLs in smokers than in nonsmokers (López-López et al. 2012b).

Conclusions
The possible association between endodontic variables and smoking is controversial. There are several epidemiological studies where no association was found (Bergström et al. 2004, Marending et al. 2005, Frisk & Hakeberg 2006, Touré et al. 2011, Rodríguez et al. 2013). On the contrary, other studies support the concept that smoking is associated with an increase in the prevalence of AP (Aleksejuniene et al. 2000, Kirkevåg & Wenzel 2003, Kirkevåg et al. 2007, Segura-Egea et al. 2008, 2011, López-López et al. 2011), being able to act as a risk factor for AP. Moreover, four epidemiological studies
have found that smoking increases the occurrence of endodontic treatment (Krall et al. 2006, Segura-Egea et al. 2008, 2011, Ojima et al. 2013). Finally, two reports concluded that endodontic treatment in smokers had fewer successes (Doyle et al. 2007) and a higher incidence of persistent AP (Kirkevang et al. 2007) compared to nonsmokers. Taking into account that most of these studies are cross-sectional and that confounding factors cannot be ruled out, further longitudinal studies are required to make firm conclusions.

**Association between endodontics and other systemic diseases**

In this paper, the scientific evidence on the association between endodontic variables and two main systemic conditions, diabetes and smoking habits, has been discussed. In another paper in this issue, the potential association between CHD and endodontics has been discussed (Cotti & Mercuro 2015). Furthermore, there are several recent investigations studying the possible relationship of other general diseases with AP and RCT.

**Hypertension**

The possible connection between hypertension and endodontic variables has been analysed. A cross-sectional study carried out in Spain to determine the prevalence of AP and RCT in hypertensive patients and control subjects concluded that no association existed between hypertension and endodontic variables (Segura-Egea et al. 2010). However, Mindiola et al. (2006) and Wang et al. (2011) reported an increased loss of RFT in hypertensive patients.

**Osteoporosis**

A cross-sectional study was conducted to determine the prevalence of AP and RCT in post-menopausal women with osteoporosis (López-López et al. 2013). Bone mineral density (BMD) of 75 post-menopausal women was measured using dual-energy X-ray absorptiometry. Three BMD groups were established (27 healthy bone group, 36 osteopenics and 12 osteoporotics), and periapical and endodontic status were assessed using digital panoramic radiographs and the PAI system (Ørstavik et al. 1986). The results demonstrated that the prevalence of AP was marginally associated with BMD (OR = 1.9; P = 0.05).

**Inherited coagulation disorders**

A cross-sectional study investigated the prevalence of endodontic variables in 58 patients with inherited coagulation disorders, such as haemophilia A or B, or von Willebrand disease, compared to 58 healthy controls (Castellanos-Cosano et al. 2013a). Results revealed that patients with inherited coagulation disorders had significantly more teeth with AP (2.2; P = 0.038) and more RFT with AP (OR = 4.00; P = 0.016), but fewer RFT (OR = 0.28; P = 0.0008).

**Chronic liver disease**

The prevalence of AP and RCT in a group of 42 patients with chronic liver disease, candidates for liver transplant, compared to 42 healthy controls, has been also studied (Castellanos-Cosano et al. 2013b). Results revealed a higher prevalence of AP (P = 0.03) and RCT (P = 0.01) in these patients, compared to healthy controls.

**Conclusions**

General diseases, such as hypertension, osteoporosis, chronic liver disease or inherited coagulation disorders, are systemic conditions with important alterations in wound healing and are associated with impaired innate immune responses. Amongst other biological mechanisms, this could be the main factor implicated in the possible connection between these systemic diseases and endodontic variables. Developing a thorough investigation on the possible association of periapical disease and endodontic treatment with systemic health status and systemic diseases of high prevalence, morbidity and mortality, such as DM or smoking habits, should be a priority of endodontic research. Such findings will surely have important implications in terms of the therapeutic approaches in these patients.

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