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REVIEW ARTICLE

Impact of systemic health on treatment outcomes in endodontics

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Abstract

Background: The healing of periapical lesions after root canal treatment (RCT) is not the result of the curative action of the treatment. The process of healing begins with inflammation, and is resolved by the clearance of the immunogen that induces the immune response. Then, the periapical tissue itself carries out the healing of the periapical lesion, by repair or by a combination of repair and regeneration, depending on the host's reparative response working properly. The ultimate objective of RCT is to achieve wound healing by removing the source of bacterial antigens and toxins, allowing chronic inflammatory tissue to become reparative tissue. Some systemic conditions increase the susceptibility of the host to infection or impair the tissue reparative response, maintaining the inflammatory process and periapical bone resorption after RCT. This can cause the failure of RCT and even the need for extraction of the affected tooth.

Objective: To analyse the scientific literature on the possible influence of systemic conditions on the treatment outcomes in endodontics, as well as to discuss the biological mechanisms that may be involved.

Methods: The search was carried out in PubMed, SCOPUS and EMBASE. The inclusion criteria established were original scientific articles reporting data about some systemic condition in relation to treatment outcomes in endodontics, including clinical studies and studies carried out in animal models.

Results: Systemic factors (age, nutrition, stress, hormones, smoking habits), and systemic diseases, such as diabetes, cardiovascular diseases, osteoporosis, HIV infection, inflammatory bowel disease, and others, can influence or interfere in the repair of periapical tissues after RCT.

Discussion: Some of these systemic diseases can alter bone turnover and fibroblast function, preventing or delaying periapical wound healing. Others can alter the microvasculature, reducing nutrients and oxygen supply to periapical tissues. As a result, these systemic conditions can decrease the success rate of RCT and provoke incomplete wound healing (typically granulomatous tissue formation) in the periapical region.

Conclusions: The results of this narrative review show worse success rate of RCT, with higher percentage of postoperative radiolucent periapical lesions and higher proportion of non-retained teeth (RFT), associated with several systemic conditions, such as smoking habits and diabetes.

KEYWORDS

diabetes, endodontic medicine, endodontic treatments, root canal treatment outcome, smoking, systemic diseases, vital pulp therapy

INTRODUCTION

The progression of the caries lesion into the dentine finally produces, when adequate restorative treatment is not carried out, inflammation of the pulp, pulp necrosis and, lastly, apical periodontitis (AP; Abbott, 2005). Restorable teeth with irreversible pulpitis or pulp necrosis with or without AP should undergo root canal treatment (RCT; Torabinejad & Walton, 2009). Given the high prevalence of AP worldwide (Tibúrcio-Machado et al., 2021), the frequency of RCT is also very high (7.4% of teeth; Jakovljevic et al., 2020). Therefore, if RCT had any influence on systemic health it would be a very important consideration. It has been almost 50 years since the focal infection theory was refuted (Ehrmann, 1977; Rogers, 1976), and in the lasts decades, based on epidemiological studies, endodontic medicine has analysed the possible impact of AP and RCT on systemic conditions, such as diabetes, cardiovascular diseases (CVDs) and others (Segura-Egea et al., 2015). Although some studies have found associations, the causation criteria (Hill, 1965) are not fulfilled and there is still no definitive scientific evidence to support the influence of RCT on systemic health (Murray & Saunders, 2000; Segura-Egea et al., 2019).

On the other hand, endodontic medicine has also analysed the possible influence of systemic health status on treatment outcomes in endodontics, mainly the outcome of RCT (Segura-Egea et al., 2015). Some systemic conditions increased the susceptibility of the host to infection, increasing microorganisms in AP and/or impairing the immune response, maintaining the inflammatory process and periapical bone resorption after RCT (Cintra et al., 2021). This can not only cause a delay in the healing of the periapical wound (Holland et al., 2017), but also persistent AP causing the failure of the RCT and even the need for extraction of the affected tooth (Olcay et al., 2018).

The ultimate objective of vital pulp therapy procedures, such as direct pulp capping and pulpotomy, is to treat teeth with compromised dental pulp without the full removal or excavation of all healthy pulp tissue aiming to preserve the health status of the remaining dental pulp (Cohenca et al., 2013). Similarly, RCT aimed the complete healing of the periapical disease, with the tooth restoration of function. The healing of pulp and periapical lesions after the endodontic treatment is not the result of the curative action of the treatment. The process of healing, both in dental pulp and periapical tissues, begins with inflammation (Goldberg et al., 2015) and is resolved by the clearance of the immunogen that induces the immune response (Childs & Murthy, 2017; Holland et al., 2017). In the case of RCT, its objective is to achieve wound healing by removing the source of bacterial antigens and toxins, allowing chronic inflammatory tissue to become reparative tissue (Trowbridge, 1990). RCT reduces the intra-canal bacterial load, seals the root canal system and prevents the passage of pulpal antigens to the periapical tissues, which allows the proliferative and the maturation phases of the healing process to take place, promoting periapical tissue repair (Childs & Murthy, 2017). Then, the healing of the periapical lesion is carried out by the periapical tissue itself, by repair or by a combination of repair and regeneration (Lin & Rosenberg, 2011). Even if the RCT has been performed optimally, avoiding the passage of immunogens to the periapical tissues, the repair of the periapical lesion will depend on the host's reparative response working properly.

The biological mechanisms involved in tissue repair are substantially influenced by genetic factors (Morsani et al., 2011) and the systemic health status of the patient (Loi et al., 2016). Therefore, genetic polymorphism and systemic factors (age, nutrition, stress, hormones, vitamin intake, hydration state and systemic diseases, such as diabetes, CVDs, osteoporosis, smoking habits and others; Holland et al., 2017), can influence or interfere in the repair of periapical tissues after RCT (Cintra et al., 2021). Some of these systemic diseases can alter bone turnover and fibroblast function, preventing or delaying periapical wound healing (Márton & Kiss, 2014). Others, can alter the microvasculature, reducing nutrients and oxygen supply to periapical tissues (Leite et al., 2008). As a result, these systemic conditions can decrease the success rate of RCT and provoke incomplete wound healing (typically granulomatous tissue

formation) in the periapical region (Sasaki et al., 2016). This is not just a possibility, the results of several studies have shown worse success rate of RCT, with higher percentage of post-operative radiolucent periapical lesions (RPL) and higher proportion of nonretained root filled teeth (RFT), in patients with systemic diseases (Cabanillas-Balsera, Segura-Egea, Bermudo-Fuenmayor, et al., 2020; Cabanillas-Balsera, Segura-Egea, Jiménez-Sánchez, et al., 2020; Nagendrababu et al., 2020; Ng et al., 2011; Segura-Egea et al., 2015, 2016).

This narrative review aimed to analyse the scientific literature on the association between systemic health status and the outcome of endodontic treatments, as well as to discuss the biological mechanisms that may be involved. Although some studies have analysed the impact of systemic factors on the outcome of vital pulp therapy procedures, the vast majority of studies have focused on the influence of systemic conditions on the outcome of RCT. Therefore, most of this narrative review will focus on that topic.

METHODOLOGY

Scale for the Assessment of Narrative Review Articles (SANRA) has been followed in the writing of this review article (Baethge et al., 2019). A literature survey was conducted to identify the articles that analyse the possible influence of the various systemic conditions on the treatment outcomes in endodontics. The search was carried out in PubMed, SCOPUS and EMBASE, using the following combinations of keywords: (endodontically treated OR RFT OR RCT OR endodontic treatment OR endodontic therapy OR vital pulp therapy OR pulpotomy OR pulp capping OR pulp revascularization OR pulp regeneration) AND (outcome OR prognosis OR persistent AP OR nonretention OR extraction OR periapical radiolucency OR periapical lesion OR failure) AND (genetic polymorphism OR diabetes OR diabetic OR smoking OR cigarette OR smoker OR cardiovascular OR hypertension OR osteoporosis OR coronary heart disease OR immunocompromised OR systemic OR nutrition OR stress OR hormones OR vitamin OR dehydration).

The inclusion criteria established were original scientific articles reporting data about some systemic condition in relation to treatment outcomes in endodontics, including clinical studies and studies carried out in animal models. Reviews, case reports, conference articles, letters to the editor and studies based on surveys or expert opinions were excluded. No language restriction was applied. Two reviewers analysed all titles and abstracts of the articles found, independently and in duplicate. Articles that did not meet the inclusion criteria were excluded. In case of disagreement between reviewers, it was resolved through debate, aiming to seek the best correlations between systemic health and the outcome of endodontic treatments.

RESULTS

Biological mechanisms connecting systemic health status with pulp and periapical repair

Wound healing by repair involves restoring damaged, still-living tissue to its normal state. By "repair" we mean that stem cells replace necrotic cells so that the tissue regains a structure similar to normal. However, the structure of the repaired dental pulp is not identical to that of the normal pulp, showing areas of fibrosis, pulp stones and areas of diffuse mineralization (Goldberg, 2011). Similarly, the repaired periapical tissue after RCT can have post-endodontic periapical fibrous scars, composed of dense fibrous collagenous tissues without inflammatory cells (Zmener et al., 2022).

Pulp and periapical wound healing requires that the immune response and the mechanisms of tissue repair and regeneration, especially bone turnover and connective tissue regeneration, function properly. The innate immune response is the first line of defence against pathogens and is essential for tissue repair processes to begin. Any systemic condition that alters the function of innate immunity cells, decreasing the chemotaxis or the phagocytic activity of neutrophils and macrophages, could delay wound healing and prevent pulp or periapical repair (Lin & Rosenberg, 2011).

Among the systemic factors that can affect the healing of pulp or periapical lesions are: genetic factors, impaired immune response, alterations in bone turnover and alterations in vascularization and oxygen supply.

Genetic factors

Tissue repair is strongly influenced by genetic factors (Morsani et al., 2011). The systemic pro-inflammatory status and the alteration of the immune response, characteristic of some systemic diseases (Lin & Rosenberg, 2011), are linked to genetic polymorphism (Fouad et al., 2020; Morsani et al., 2011; Salles et al., 2018). The outcome of vital pulp therapy procedures and RCT is related closely to the host immune and reparative responses, which depend on the differentiation and function of specialized cells, such as macrophages, neutrophils, lymphocytes, fibroblasts

and osteoblasts, orchestrated by growth factors, cytokines, enzymes, transcriptional factors and other regulatory molecules (Aminoshariae & Kulild, 2015). Polymorphisms of genes encoding for molecules implicated in immune and reparative responses, result in altered gene expression and functional variations of the encoded molecules (Cintra et al., 2021). Individuals with specific genotypes could be more susceptible to AP or could present an increase in disease severity (Aminoshariae & Kulild, 2015; Morsani et al., 2011). Similarly, some genetic polymorphisms are associated with a worse RCT outcome, delayed periapical repair and persistent AP. Gene polymorphism in the minor allele of an IL1B variant (allele2 of IL-1B) is linked to persistent AP (Morsani et al., 2011). This gene polymorphism increase IL-1β production and could influence host response and enhance inflammatory reactions in the pathogenesis of endodontic failure, contributing to increased susceptibility to persistent AP (PAP; Salles et al., 2018). However, one other study has not found an association (Siqueira et al., 2009). On the contrary, the results of the latter study suggest that allele H131 of the FcγRIIA gene and a combination of this allele with allele NA2 of the FcγRIIIB gene are associated with persistent AP (Fouad et al., 2020; Siqueira et al., 2009). Nuclear factor kappa B (RANK) and receptor activator of nuclear factor kappa B ligand (RANKL) genetic polymorphisms have been also associated with PAP (Petean et al., 2019). Subjects who carry the RANK T allele have a lower risk of having persistent AP. In RANKL polymorphism, the genotype distribution is different in patients with persistent AP compared to healed groups. Single nucleotide polymorphisms (SNPs) in the encoding genes BMP2, BMP4, SMAD6 and RUNX2 have been also associated with persistent AP (Küchler et al., 2021). The interactions between rs235768 in BMP2 and rs59983488 in RUNX2 and between rs17563 in BMP4 and rs2119261 in SMAD6 are associated with PAP, suggesting that an interplay of these SNPs is involved in the development of persistent AP and worse RCT outcome. Finally, polymorphisms in the promoter region of defensin beta 1 (DEFB1) genes have been shown to be associated with the development of post-treatment persistent AP (Antunes et al., 2021).

Additional studies have investigated the possible association of other genetic polymorphisms with the outcome of RCT, concluding that polymorphism in the CD14 and TLR4 genes (Rôças et al., 2014) nor polymorphism in the FcγRIIIa (Siqueira et al., 2011) gene do not influence the response to endodontic treatment of teeth with AP.

In addition to being related to a higher percentage of endodontic treatment failures, genetic polymorphisms may be behind numerous associations that epidemiological studies have found between endodontic pathosis and systemic diseases.

Impaired immune response

Some systemic conditions, such as cardiovascular disease, diabetes mellitus (DM), tobacco smoking, hypertension, inherited coagulation disorders and osteoporosis, can impair the nonspecific immune system and alter pulp and periapical healing after endodontic treatment (Segura-Egea et al., 2015).

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 (Ng et al., 2011; Segura-Egea et al., 2015). Innate immunity is the first line of defence against pathogens. Systemic conditions altering innate immunity cell functions, decreasing neutrophil phagocytosis or macrophage chemotaxis, result in an inflammatory state that impairs host cellular proliferation, delaying wound healing and preventing periapical repair.

Systemic diseases in which a stronger systemic inflammatory reaction is induced, with activation of NF-κβ in macrophages and increased cellular oxidant stress, can alter bone turnover and periapical wound healing (Taylor et al., 2013). These clinical situations are characterized by increased C-reactive protein levels in serum and the release of potentially tissue-destructive substances such as reactive oxygen species, collagenase, serine proteases and upregulation of pro-inflammatory cytokines (IL-1b, IL-6, IL-8, IL-10, TNF-α). All these biological changes result in further progression of the periapical inflammation and impaired periapical healing.

On the other hand, immunity disorders, especially HIV (human immunodeficiency virus) infection and AIDS (acquired immunodeficiency syndrome), that affects T lymphocytes, involved in periapical repair (Trowbridge, 1990), could also influence the outcome of endodontic treatments (Aminoshariae et al., 2017).

Fibroblast dysfunction and alterations in bone turnover

Systemic diseases in which there is an alteration in bone turnover, such as increased osteoclastic activity or osteoblast and fibroblast dysfunction, with increased bone resorption and altered collagen synthesis, could also prevent or delay periapical wound healing (López-López et al., 2015; Taylor et al., 2013). This occurs in systemic

diseases that induce a large inflammatory reaction. The activation of NF-κβ in macrophages and the increased cellular oxidant stress, alter bone turnover and delay wound healing (Taylor et al., 2013).

These clinical situations are characterized by increased C-reactive protein levels in serum and the release of potentially tissue-destructive substances such as reactive oxygen species, collagenase, serine proteases and upregulation of pro-inflammatory cytokines (IL-1b, IL-6, IL-8, IL-10, TNF-α; Cintra et al., 2016; Gomes et al., 2013). This results in further progression of the periapical inflammation and impaired periapical healing.

Alterations in vascularization and oxygen supply

It is worth noting that alterations at the level of vascularization and oxygen supply could also affect pulp and periapical repair. Some systemic diseases or conditions, such as smoking, alter, morphologically and/or functionally, the microvasculature and so reduce blood flow and decrease the supply of nutrients and oxygen (Kinane & Chestnutt, 2000; Segura-Egea et al., 2015). Diabetes interferes tissue nutrition and can impair dental pulp metabolism, reducing nutrients and oxygen supply to pulp tissues (Leite et al., 2008).

When any of these mechanisms interrupt pulp or periapical repair, inflammation persists and the lesion remains uncured, becoming chronic (Trowbridge, 1990). In the case of the root filled tooth, PAP occurs, which results in loss by extraction.

Systemic conditions associated with poor prognosis of endodontic treatments

Animal and epidemiological studies have provided data suggesting that several systemic conditions, including diabetes, CVDs, smoking habits, menopause/osteoporosis, HIV infection, inflammatory bowel disease and others, can influence the prognosis of endodontic treatments (Cintra et al., 2021; Segura-Egea et al., 2015).

Diabetes

Diabetes mellitus is a 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. Diabetes is associated with devastating complications, such as retinopathy, nephropathy, neuropathy, vascular disease and impaired wound healing. In diabetics, metabolic glycaemic control is performed by determining the glycated haemoglobin (HbA1c; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2000). HbA1c levels less than or equal to 6.5% are the goal for optimal glycaemic control in diabetic patients.

The first studies regarding the possible association of diabetes with the outcome of endodontic treatments date back to the mid-20th century. Bender and Seltzer (1963) reported that if proper insulin therapy was not introduced prior to RCT, periapical healing will not take place and, in fact, the initial lesion may increase in size despite RCT. However, studying a series of 33 well-controlled diabetic patients, they found that endodontic procedures were just as successfully in diabetic patients as in normal control patients. Since then, many experimental animal and human epidemiological studies have investigated the relationship between diabetes and endodontic treatment and pathology.

Experimental studies in rats and mice (Astolphi et al., 2015; Bain et al., 2009; Cintra, Samuel, Azuma, et al., 2014; Fouad et al., 2002; Garber et al., 2009; Kodama et al., 2011; Tavares et al., 2017) have concluded that diabetic animals have more pronounced pulp and periapical inflammation, with larger periapical lesions (Fouad et al., 2002; Iwama et al., 2003); accelerated development and progression of AP (Cintra, Samuel, Facundo, et al., 2014); inhibition of dentine bridge formation after direct pulp capping (Garber et al., 2009). All these findings suggest that diabetes alters tissue repair mechanisms at the pulp and periapical levels, interfering with healing after endodontic treatment. However, an study did not find significant difference between the induction of dentine bridge formation in diabetic and healthy controls rats after direct pulp capping with silicate-based cements (Madani et al., 2014).

Clinical and epidemiological studies conducted in humans analysing the association between diabetes and the prevalence of AP and RCT treatment also provide data that suggest the influence of diabetes to create a worse outcome of endodontic treatments, especially RCT (Segura-Egea et al., 2019).

The literature reveals delayed periapical healing in diabetic subjects, lower rates of repair associated with RFT (Arya et al., 2017; Bender & Seltzer, 1963; Laukkanen et al., 2019), slower reduction in the size of periapical lesions in poorly controlled diabetic patients (Cheraskin & Ringsdorf, 1968) and greater percentage of PAP in diabetics, compared to control subjects (Britto et al., 2003; Falk et al., 1989; Ferreira et al., 2014; Fouad & Burleson, 2003;

Limeira et al., 2020; López-López et al., 2011; Marotta et al., 2012; Segura-Egea et al., 2005; Smadi, 2017). Some of the epidemiological studies have determined the strength of the association by calculating the odds ratio values, which are not constant and are not always significant (Table 1, top). However, the OR values calculated for the outcome of RCT in diabetics and control subjects, ranged from 1.1 to 7.2, indicating that the outcome of RCT could be considered moderately associated with the diabetic state.

Two prospective studies that have compared the outcome of RCT in diabetic and control subjects (Arya et al., 2017; Rudranaik et al., 2016) also supported this statement. A first study compared the success of primary RCT between type 2 diabetic and nondiabetic patients, finding a significantly less periapical healing in the diabetic group (43%) compared with the nondiabetic group (80%; $p < .05$) after 12-month follow-up (Arya et al., 2017). A second prospective study aimed to evaluate the clinical and radiographic healing outcome of single visit RCT in type 2 DM patients with periapical disease (Rudranaik et al., 2016), concluding that type 2 diabetics had chronic and larger sized lesions when compared to control subjects, with the clinical and radiographic healing outcome of single visit RCT delayed in diabetic patients.

This topic has been also analysed by two systematic reviews and meta-analysis. A first systematic review concluded that diabetics have significantly higher prevalence of RFT with RPL (OR = 1.4; 95% CI = 1.1–1.8; $p = .006$; Segura-Egea et al., 2016). A subsequent systematic review, including the same cross-sectional studies, obtained the same results (Gupta et al., 2020). However, in this last review the meta-analysis of the two mentioned prospective studies (Arya et al., 2017, Rudranaik et al., 2016) was carried out, providing an OR = 6.4 (95% CI = 1.9–21.0; $p = .002$), suggesting a strong connection between the presence of periapical radiolucency on RFT and diabetes.

The results of other studies also support the concept that diabetes influences the outcome of RCT impairing periapical wound healing. Thus, a study aiming to investigate the impact of systemic health and tooth-based factors on the outcome of RCT concluded that, although tooth-based factors had a more profound impact on the outcome of RCT, diabetes diminished the success of RCT, especially in teeth with AP (Laukkanen et al., 2019).

The evaluation of the fractal dimension (FD) changes in radiographs of periapical lesions using a fractal analysis in healthy individuals and type 2 diabetes mellitus (DM) patients following RCT has showed that diabetes had a negative effect on FD increase (Uğur Aydın et al., 2021).

Another retrospective observational study has been conducted comparing the outcome of RCT in diabetic patients and control subjects, showing a significantly lower success rate following RCT in diabetics (Martinho et al., 2021). The same authors carried out an experimental study using Wistar rats, finding that diabetic rats with increased AP had angiogenic deficits and impaired tissue repair. The authors concluded that impairment of the angiogenic process in diabetic animals could be implicated in the failure of RCT.

On the other hand, several studies, one retrospective (Mindiola et al., 2006) and two prospective (Marending et al., 2005; Wang et al., 2011) have investigated the association between diabetes and the prevalence of extracted RFT, finding a decreased survival of RFT, with significantly higher prevalence of extracted RFT in diabetic

TABLE 1 Prevalence of RFT with AP (top) and prevalence of extracted RFT (bottom) in control subjects and diabetic patients

Study	Controls (%)	Diabetics (%)	OR (CI 50%)	*p*
Falk et al. (1989)	21	26	1.3 (0.9–2.1)	.20
Fouad and Burleson (2003)	31	36	1.2 (0.7–2.1)	.42
Britto et al. (2003)	44	46	1.1 (0.5–2.6)	.82
Segura-Egea et al. (2005)	60	83	3.3 (0.5–37.9)	.17
López-López et al. (2011)	24	46	2.7 (0.8–10.1)	.09
Marotta et al. (2012)	38	46	1.4 (0.8–2.4)	.21
Ferreira et al. (2014)	20	43	3.1 (0.8–12.5)	.06
Smadi (2017)	19	28	4.1 (2.0–8.3)	.02*
Limeira et al. (2020)	8	52	7.2 (2.5–20.9)	<.01*
Mindiola et al. (2006)	3.9	10.3	Not provided	<.001*
Wang et al. (2011)	3.0	5.3	1.8 (1.5–2.1)	<.001*
Ng et al. (2011)	4.4	15.6	3.2–3.4 (HR)	<.001*

Abbreviations: AP, apical periodontitis; HR, hazard ratio; OR, odds ratio; RFT, root filled teeth.

*Significant *p* value.

patients compared to nondiabetic subjects (Table 1, bottom). A systematic review (Cabanillas-Balsera et al., 2019) concluded that available studies indicate a significant relationship between diabetes and increased frequency of nonretained RFT (OR = 2.4; 95% CI = 1.5–3.9; $p = .001$).

An umbrella review concluded that DM is associated with the outcome of RCT and can be considered as a preoperative prognostic factor (Nagendrababu et al., 2020).

Several well-known biological mechanisms explain how poorly controlled diabetes could impair pulp (Bender & Bender, 2003) and periapical repair after endodontic treatments (Segura-Egea et al., 2015; Figure 1). Hyperglycaemia and dyslipidaemia cause immune dysfunction (Garber et al., 2009). Neutrophil phagocytosis is decreased and macrophages are upregulated, with increased production of pro-inflammatory cytokines (Lima et al., 2013). Advanced glycated end products (AGEs) that hyperglycaemia provokes, bind to collagen decreasing osteoblastic differentiation and bone formation (Li et al., 2014). Hypercalcemia status provoke apoptosis of osteoblasts and fibroblasts, inhibition of collagen production and inhibition of osteoblastic cell proliferation and differentiation (Li et al., 2014). Moreover, AGEs interact with specific receptors in macrophages (RAGE) activating NF-κβ, increasing cellular oxidant stress and upregulating pro-inflammatory cytokines (Lima et al., 2013). 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). Finally, hyperglycaemia modulates the RANKL/OPG ratio, directly and indirectly via the AGE/RAGE axis, increasing osteoclastic activity and bone resorption, inclining the balance towards enhanced inflammation and destruction (Serrão et al., 2017). Thus, poorly controlled diabetes predisposes to chronic inflammation, diminishes tissue repair capacity and delays wound healing. In inflamed periapical tissues of RFT, diabetes compromises the immune response aggravating periapical inflammation and impairing bone turnover and wound healing, increasing the prevalence of post-treatment AP.

On the other hand, genetic polymorphism can also explain the association found in epidemiological studies between the outcome of RCT and diabetes. It has been described that the polymorphism of the RANK and RANKL genes is associated with both a higher prevalence of PAP (Petean et al., 2019) and type 2 diabetes (Duan et al., 2016).

The intake of oral hypoglycaemic agents, very frequent in diabetic patients, especially in type 2, is not related to a worse result of RCT (Jahreis et al., 2019).

Cardiovascular diseases

Cardiovascular diseases are a group of disorders of the heart and blood vessels and include coronary heart disease (CHD), cerebrovascular disease, rheumatic heart disease and other conditions (https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1, accessed 6-05-2022), with hypertension and CHD as the most prevalent CVD. Hypertension (HTN) or high blood pressure is a chronic medical condition in which the blood pressure in the arteries is elevated. Persistent HTN is one of the risk factors for stroke, heart attacks, heart failure and arterial aneurysm and is a leading cause of chronic kidney failure. CHD encompasses a range of heart disease whose origin lies in the inability of coronary arteries to supply sufficient blood needed for a given territory of the heart muscle, which results in less oxygen to the heart and greater accumulation of metabolites (Muñoz et al., 2008).

Since the pioneer studies of Mattila and colleagues (Mattila, 1993; Mattila et al., 1989, 1995), several studies have reported an association between dental infections and a higher prevalence of cardiovascular events (Jansson et al., 2001; Oikarinen et al., 2009; Willershausen et al., 2009). In addition, three longitudinal studies have also found a positive association between AP and CVD (Caplan et al., 2006; Gomes et al., 2016; Jansson et al., 2001), and several cross-sectional studies have demonstrated that RPL are significantly more prevalent in patients with CVDs (An et al., 2016; Costa et al., 2014; Grau et al., 1997; Liljestrand et al., 2016; Messing et al., 2019; Pasqualini et al., 2012; Virtanen et al., 2017). However, none of these studies differentiated between RFT and nonendodontically treated teeth. Therefore, no conclusions can be drawn regarding the possible influence of CVDs on the healing of periapical lesions after RCT. Two studies have found higher prevalence of RPL in hypertensive patients, but they found no difference between hypertensive and control patients in the prevalence of RPL in RFT (Segura-Egea et al., 2010, 2011). In contrast, a retrospective cohort study analysed the development of AP in RFT with and without periodontal disease, taking into consideration various factors. They found that periodontal condition and hypertension were the sole significant factors associated with the presence of RPL in RFT (Ruiz et al., 2017).

The only existing data in the scientific literature indicating a negative influence of hypertension on the outcome of RCT are two studies finding a significantly greater loss of RFT by extraction in hypertensive patients (Mindiola et al., 2006; Wang et al., 2011).

Regarding the biological mechanism that could explain an influence of CVDs on the outcome of endodontic

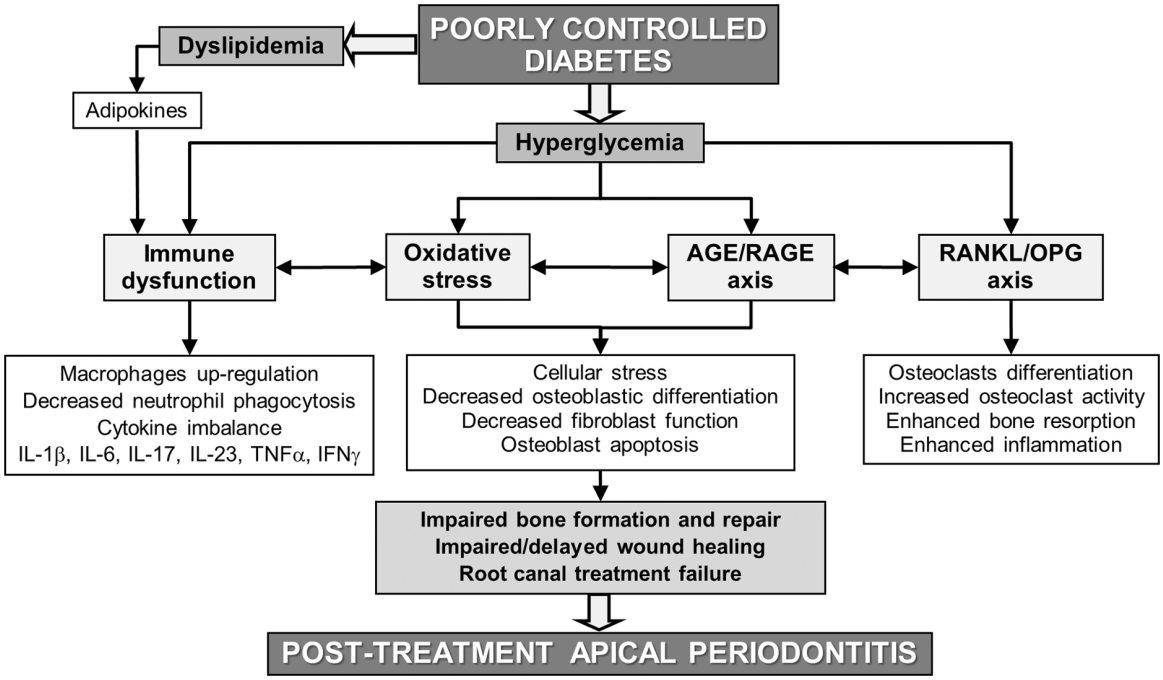

FIGURE 1 Network of potential mechanisms by which poorly controlled diabetes could impair periapical lesion repair after endodontic treatment.

treatments, an experimental study carried out in rats evaluated the effect of hypertension on tissue response to and mineralization capacity of white and grey mineral trioxide aggregate, using polyethylene tubes containing grey MTA or white MTA implanted into the dorsal connective tissue. The results showed that hypertension undermines tissue repair and mineralization, which can negatively affect treatment outcome (Martins, Sasaki, et al., 2016). In models of hypertension, a greater differentiation of osteoclasts has been observed *in vitro*, however, in an *in vivo* model, an influence in periapical lesion development was not detected (Martins, Gomes-Filho, et al., 2016).

As in the case of diabetes, AP shares with CVDs genetic risk factors. Genetic polymorphism increases susceptibility to chronic inflammation, modulating systemic pro-inflammatory mediators, which could favour both persistent chronic AP and CVDs. Polymorphisms in IL-1B gene are associated with both AP (Salles et al., 2018) and myocardial infarction (Bis et al., 2008). Similarly, SNP in KCNK3 is involved in increased susceptibility to hypertension as well with AP (Messing et al., 2019).

On the other hand, both diseases also share environmental risk factors, such as diabetes and smoking, which in addition to contributing to inflammatory susceptibility, have direct influence at the periapical and cardiovascular levels (Segura-Egea et al., 2015).

Atherosclerosis, directly related to CVDs, is not associated with the presence of RPL in RFT (Petersen et al., 2014).

Smoking habits

Tobacco use is associated with a systemic condition that implies a well-established risk factor for systemic and oral health, increasing the risk of caries (Fure, 2004) and periodontal disease (Walter, Kaye, et al., 2012). Tobacco smoking has harmful effects on periodontal bone (Krall et al., 1999), and major effects on the host response to infections, with a long-term chronic effect on the inflammatory response 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 demonstrated that there are lower levels of cytokines, enzymes and possibly polymorphonuclear cells in smokers (Palmer et al., 2005).

As a result, defensive and reparative responses of dental pulp tissue are decreased in smokers (Ghattas Ayoub et al., 2017) and, at the periapical level, the process of periapical bone destruction could be greater in smokers, who could also have an altered periapical repair after RCT, with a consequent increase in the number and/or size of periapical lesions (Segura-Egea et al., 2015).

The scientific literature contains conflicting evidence relating smoking habits and AP or RCT (Aminoshariae et al., 2020; Duncan & Pitt Ford, 2006; Segura-Egea et al., 2015; Walter, Rodriguez, et al., 2012). There are many studies that have found a significant association

between smoking and the prevalence of periapical lesions of endodontic origin (Aleksejuniene et al., 2000; Doyle et al., 2007; Kirkevang et al., 2007, 2017; Kirkevang & Wenzel, 2003; Krall et al., 2006; López-López et al., 2012; Oginni et al., 2015; Persic Bukmir et al., 2019; Segura-Egea et al., 2008, 2011). A systematic review concluded that smokers have a prevalence of AP and RCT that is greater than 2.5 times higher than nonsmokers (Pinto et al., 2020). Several studies have also found that smoking is associated with higher prevalence of RCT (Segura-Egea et al., 2008, 2011; Sopińska & Bołtacz-Rzepkowska, 2020). RCT has been shown to be almost two times more prevalent in smokers, with a dose–response relationship (Krall et al., 2006). However, other studies found no association between smoking and the prevalence of AP (Bergström et al., 2004; Frisk & Hakeberg, 2006; Rodriguez et al., 2013) or the frequency of RCT (Bergström et al., 2004; Persic Bukmir et al., 2019).

Regarding the possible influence of smoking in the outcome of RCT, several cross-sectional studies have not found an association between smoking and the presence of RPL in RFT (Marending et al., 2005; Segura-Egea et al., 2008, 2011; Sopińska & Bołtacz-Rzepkowska, 2020; Table 2, top). On the contrary, the study of Jansson (2015) reported a significant correlation between smoking and the prevalence of RFT with AP. In addition, a retrospective longitudinal and machine learning study has showed that smoking is significantly associated with risk of RCT failure (Herbst et al., 2022). Finally, three retrospective studies found that RCT in smokers had fewer successes and more failures than in nonsmoker patients (Doyle et al., 2007; Khalighinejad et al., 2017; Kirkevang et al., 2007; Table 2, bottom). Another study investigated the effect of smoking on the status of the apical region in properly RFT, with and without periodontal involvement, found a noticeable negative effect of smoking on the severity and prognosis of AP and this negative effect worsened when it was accompanied by marginal periodontitis (Mahmood et al., 2019).

Two systematic reviews with meta-analysis have analysed the association of smoking habits with the prevalence of RPL in RFT (Cabanillas-Balsera, Segura-Egea, Jiménez-Sánchez, et al., 2020) and with the occurrence of RFT extraction (Cabanillas-Balsera, Segura-Egea, Bermudo-Fuenmayor, et al., 2020). These systematic reviews concluded that low evidence indicates that RFT of smoking patients are three times more likely to be extracted (OR = 3.4; 95% CI = 1.2–10.1; $p = .02$; Cabanillas-Balsera, Segura-Egea, Bermudo-Fuenmayor, et al., 2020), and moderate quality scientific evidence indicates a weak but significant relationship between smoking and the prevalence of RPLs in RFT (OR = 1.2; 95% CI = 1.1–1.3; $p < .001$; Cabanillas-Balsera, Segura-Egea, Jiménez-Sánchez, et al., 2020).

In relation to periapical wound healing after endodontic surgery, the success rate 1 year after apical surgery is similar in smokers and nonsmokers subjects (Öğütlü & Karaca, 2018; Sutter et al., 2020).

The possible mechanisms by which tobacco could alter the immune and reparative response, influencing pulp and periapical inflammation and repair, are summarized in Figure 2 and were reviewed by Segura-Egea et al. (2015). Smoking:

a. decreases blood and oxygen supply and causes endothelial cell injury because of free radicals (Lehr, 2000),
b. alters collagen synthesis by fibroblasts, impairing tissue repair (Raulin et al., 1988; Wong & Martins-Green, 2004),
c. increases RANKL / osteoprotegerin ratio in saliva and in serum with bone loss exacerbation (Johannsen et al., 2014),
d. alters the immune response by suppressing the functions of polymorphonuclear leukocytes, macrophages,

TABLE 2 Prevalence of RFT with AP (top) and prevalence of extracted RFT (bottom) in control subjects and smokers

Study	Controls (%)	Smokers (%)	OR (CI 50%)	*p*
Marending et al. (2005)	Not provided	Not provided	0.8 (0.1–7.9)	>.05
Segura-Egea et al. (2008)	37	40	1.2 (0.5–2.6)	>.05
Segura-Egea et al. (2011)	39	39	1.0 (0.3–3.1)	>.05
Jansson (2015)	37	41	1.2 (1.1–1.3)	<.001*
Sopińska and Bołtacz-Rzepkowska (2020)	36	38	1.1 (0.9–1.3)	>.05
Herbst et al. (2022)	Not provided	Not provided	2.1 (1.2–3.5)	<.05*
Doyle et al. (2007)	3.2	18.4	6.9 (2.1–23.2)	<.001*
Kirkevang et al. (2017)	Not provided	Not provided	1.1 (0.8–1.5)	>.05
Khalighinejad et al. (2017)	16.5	27.9	2.2 (1.3–3.8)	<.01*

Abbreviations: AP, apical periodontitis; HR, hazard ratio; OR, odds ratio; RFT, root filled teeth.

*Significant *p* value.

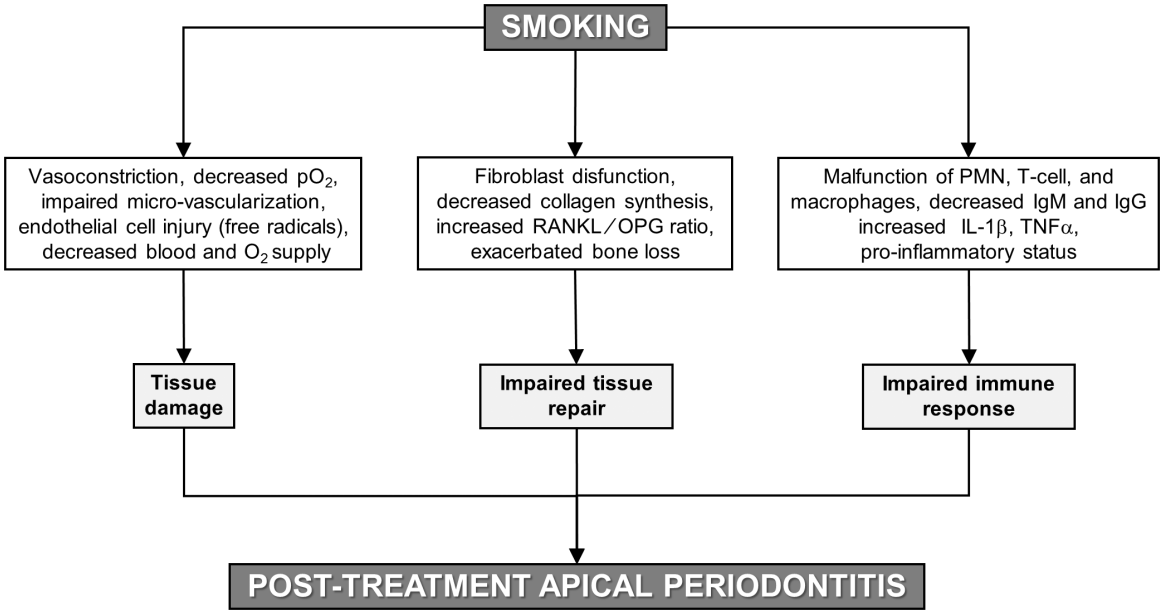

FIGURE 2 Network of potential mechanisms by which tobacco smoking could affect the periapical status.

T-cell lymphocytes and reducing the levels of antibodies (Johnson & Hill, 2004; Palmer et al., 2005) and.

e. induces a stronger chronic systemic inflammatory response (Barbieri et al., 2011; Johannsen et al., 2014).

Menopause/osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration, with increased bone fragility and susceptibility to bone fracture. Although changes in bone mass and calcium metabolism are already evident in the premenopausal period, at menopause, the production of oestrogens decreases drastically while follicle-stimulating hormone levels rise sharply in parallel, leading to osteoporosis in skeletal bones (Sun et al., 2006). Therefore, the menopause marks the beginning of bone loss that continues until the end of life. Loss of bone mass, *per se*, does not cause symptoms but, once a fracture does occur, pain, loss of function and, in some cases, deformity may result (Sultan & Rao, 2011). Several have reported that bone changes in osteoporosis were associated with loss of periodontal attachment, loss of teeth and reduction of the height of the residual alveolar bridge (Brennan et al., 2007). Almost 60 years ago, Bender and Seltzer (1963) suggested that osteoporosis may help to explain why healing following root canal therapy was more favourable in the younger age groups, and the number of failures was larger among the women.

Very few studies have analysed the effect of osteoporosis on periapical bone healing after RCT. López-López et al. (2015) investigated the relationship between RPL and bone mineral density in post-menopausal women, finding that low bone mineral density was marginally associated with a higher frequency of RPL; 25% of osteopenic and osteoporotic women showed at least one radiolucent periapical lesion, whereas this percentage was only 7.4% in the control group. Another study investigated the prevalence of periapical lesions in patients with osteoporosis, compared with the general population of the hospital, finding that the prevalence of periapical lesions was significantly higher in osteoporotic patients (Katz & Rotstein, 2021).

Bisphosphonates are antiresorptive drugs used in the treatment of metabolic bone disorders, such as osteoporosis and metastatic bone cancer. These drugs work through the inhibition of osteoclast formation and activity and shortening osteoclast lifespan (Rizzoli et al., 2008). Considering that ostecoclasts play a key role in bone remodelling, an integral component of the process of progression and healing of a periapical lesion, bisphosphonates could affect the healing of periapical lesions. This hypothesis was investigated in a case–control study that evaluated the outcome of RCT in patients taking oral bisphosphonates, compared with control patients (Hsiao et al., 2009). The results showed that patients taking long-term oral bisphosphonates can expect a satisfactory outcome with evidence of periradicular healing after conventional RCT. Another study assessed the difference in the prevalence of periapical lesions in patients treated with two types of nitrogen-containing bisphosphonates alendronate and risedronate (Katz & Rotstein, 2021); the results showed a marked reduction in the prevalence of periapical lesions, especially when risedronate was used.

AIDS and HIV infection

HIV (human immunodeficiency virus) infection is characterized by opportunistic infections and decreased CD4+ lymphocyte counts. If left untreated, HIV can lead to the disease AIDS (Shetty et al., 2006). Taking into account that during the development of periapical lesions, the infiltrated number of different types of T cells and the secretion of T-cell-related cytokines in the region of root apex reflected the inflammatory status of periapical lesions and correlated with the periapical bone destruction (Wang et al., 2022), HIV patients could have impaired periapical repair.

Several studies have analysed the outcome of RCT in HIV-positive patients and control subjects. A retrospective study evaluated the success rate of nonsurgical RCT in 157 HIV-positive patients; after 6-month follow-up, a success rate of 90% was observed in the study group, without statistically significant differences with controls (Shetty et al., 2006). Another retrospective study compared the rate of successful RCTs between two cohorts of patients with similar teeth, one group with HIV/AIDS and one without. There was no statistically significant difference in endodontic success between the two groups (Alley et al., 2008). Similar results were observed in two other prospective studies with 12 months follow-up (Quesnell et al., 2005) and 24 months follow-up (Tootla & Owen, 2012). A retrospective study with 26 months follow-up concluded that endodontic therapy had a relatively high degree of success in the majority of HIV/AIDS patients (Suchina et al., 2006).

Inflammatory bowel disease

The term inflammatory bowel diseases (IBD) groups two chronic recurrent inflammatory processes of the gastrointestinal tract, Crohn's disease (CD) and ulcerative colitis (UC) characterized by diffuse inflammation of the intestinal mucosa causing clinical episodes of intestinal inflammation (Baumgart & Sandborn, 2012). Oral manifestations are found in approximately 10% of patients with IBD, including angular cheilitis, mucosal oedema, linear ulceration and granulomatous gingivitis (Kalmar, 1994), also presenting a higher prevalence of caries (Brito et al., 2008) and periodontal disease (Koutsochristou et al., 2015).

A clinical study investigated the healing after nonsurgical primary/secondary RCT of AP in patients with inflammatory bowel disease (IBD) treated with anti–TNF-α biologic medications (BMs) and reported that the treatment of AP in patients taking BMs had no complications and was associated with faster healing than the control (Cotti et al., 2018). The authors suggested that BMs could be used in the treatment of AP. At this respect, two case–control studies have found a higher prevalence of AP in patients with IBD (Poyato-Borrego et al., 2020; Segura-Sampedro et al., 2022) compared to control subjects. On the contrary, a cross-sectional study reported no association between the prevalence of AP and IBD (Piras et al., 2017). Some studies have analysed the prevalence of RFT with AP in patients with IBD and control subjects, with controversial results. A prevalence study reported similar prevalence of RFT with RPL in patients with UC (31%) or Crohn's disease (21%; $p > .05$; Poyato-Borrego et al., 2021), and a first age- and gender-matched case–control study found no significant differences between IBD patients and controls (Poyato-Borrego et al., 2020). However, the results of a recent age- and sex-matched case–control study (Segura-Sampedro et al., 2022), reported that the percentage of IBD patients with at least one RFT with AP was 54%, compared to only 11% in the control group (OR = 9.60; 95% CI = 2.35–39.35; $p = .001$). The authors concluded that dentists should monitor the evolution of periapical lesions of root treated teeth in patients with UC or Crohn's disease.

Others

In the search carried out, studies have been found investigating the possible association of other systemic conditions, such as inherited coagulation disorders (Castellanos-Cosano, Machuca-Portillo, Sánchez-Domínguez, et al., 2013), patients with cirrhosis (Grønkjær et al., 2016), liver transplant candidates (Castellanos-Cosano, Machuca-Portillo, Segura-Sampedro, et al., 2013), with endodontic infections and the outcome of endodontic treatments, especially RCT, but their low number prevents drawing concrete conclusions regarding the relationship of these diseases with the result of endodontic treatments.

CONCLUSIONS

This study addressed systemic factors that may interfere with endodontic treatment outcomes. The studies discussed in this review show the importance of knowledge about the systemic health of our patients to assist in the preparation of a correct and predictable treatment plan. It was clear that the reduction in bacterial load of root canals associated with the use of good filling materials and the host's immune response are able to act on the residual microorganisms of the root canals and favour the repair of periapical lesions. On the other hand, it was also clear that the individual's systemic condition could interfere in this process. Thus, this study showed

the importance of knowledge of systemic factors for the endodontist to provide comprehensive patient care, and for the interaction between dentists and doctors, providing favourable conditions for oral and systemic health to patients.

AUTHOR CONTRIBUTIONS

J.J.S.-E. and L.T.A.C. involved in conceptualization; D.C.-B. & J.M.-G. involved in methodology and software; J.J.S.-E., J.M.-G. and D.C.-B. involved in validation; J.J.S.-E. and D.C.-B. involved in formal analysis; J.J.S.-M., J.M.-G. and D.C.-B. involved in investigation; J.J.S.-E. and D.C.-B. involved in data curation; J.J.S.-E. & L.T.A.C. and D.C.-B. wrote and prepared the original draft; D.C.-B., L.T.A.C., J.M.-G. & J.J.S.-E. reviewed and edited the manuscript; J.J.S.-E. and L.T.A.C. supervised the work. All authors have reviewed and approved the submitted version. All authors developed the idea and contributed to the final version of the manuscript equally.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated

ETHICAL APPROVAL

This narrative review did not need the Ethics Committee Approval due to the absence of research with patients.

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