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REVIEW ARTICLE

Evolution of endodontic medicine: a critical narrative review of the interrelationship between endodontics and systemic pathological conditions

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Abstract

Endodontics has gained emphasis in the scientific community in recent years due to the increase in clinical and in animal models studies focused on endodontic medicine, which aims to evaluate the interrelationship between systemic and periapical tissues pathological conditions. These studies have shown that systemic changes can boost the pathogenesis of endodontic infection, favoring its development and progression. A contrary relationship is reported in numerous studies that affirm the potential of endodontic infection to trigger systemic damage and may lead to the worsening of pre-existing pathologies. Recently, the potential of filling materials to develop systemic changes such as neurological alterations had been evaluated, also showing that systemic diseases can negatively influence tissue responses to filling materials after endodontic treatment. Despite advances in endodontic medicine studies, there are still gaps in knowledge on the mechanisms of interactions between apical periodontitis (AP) and systemic diseases and much research to be done. In this sense, this critical narrative literature review aimed to show the evolution of studies in endodontic medicine to help the endodontist to know the role of systemic diseases in the pathogenesis of AP and the possible interference in the repair of periapical tissues after endodontic treatment, as well as to evidence the systemic complications that can be triggered or aggravated in the presence of endodontic infection.

Keywords Apical periodontitis · Dental pulp necrosis · Endodontic · Oral health · Root canal filling materials

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Introduction

Apical periodontitis (AP) is a lesion resulting from the presence of endodontic infection. It is estimated that half of the world population has at least one tooth with apical periodontitis [1]. Due to this injury being extremely common, historically, many speculations have been made in order to assess the possible systemic impacts that apical periodontitis can cause [2–4].

In 1891, Miller studies showed the presence of bacteria in dental pulp [5] and the idea became popular that the dental pulp would be a source of infection that could help to spread bacteria throughout the body, causing disease or even leading to death [2]. Clinical case reports were published at this time demonstrating the cure of diseases after tooth extraction [6, 7]. The theme was known as "focal infection theory" [2–4].

One of the main treatments for many diseases at that time was the multiple extraction of teeth with the aim of trying to "eliminate" the source of bacteria that were considered the cause of the diseases [6, 7]. Over time, it was observed that, in addition to not improving the clinical condition, multiple tooth extractions determined other health problems such as dyspepsia [8]. In addition, it was observed that diseases supposedly caused by teeth were also common in patients with healthy teeth. Then, the theory of focal infection was totally discredited [9].

In general, patients with systemic problems have alterations in blood cells and inflammatory mediators, and may respond more exacerbated in the presence of endodontic infection [10, 11]. On the other hand, studies have shown that the presence of AP can also influence the pathogenesis of systemic disorders [12–15]. This is mainly because in the scenario of AP there is a massive release of cells and inflammatory mediators (Fig. 1). As it is common for this lesion to remain long periods without treatment, since there are often no symptoms, these cells and mediators are constantly released into the bloodstream and can reach places where there are other pathological processes of systemic diseases [12–15]. The more mediators that activate the inflammation, the greater the potentiation of the pathological process.

Based on the above considerations, it is observed that the link between endodontics and systemic health cannot be disregarded by the professional in his clinical practice. This review will address (1) effects of apical periodontitis

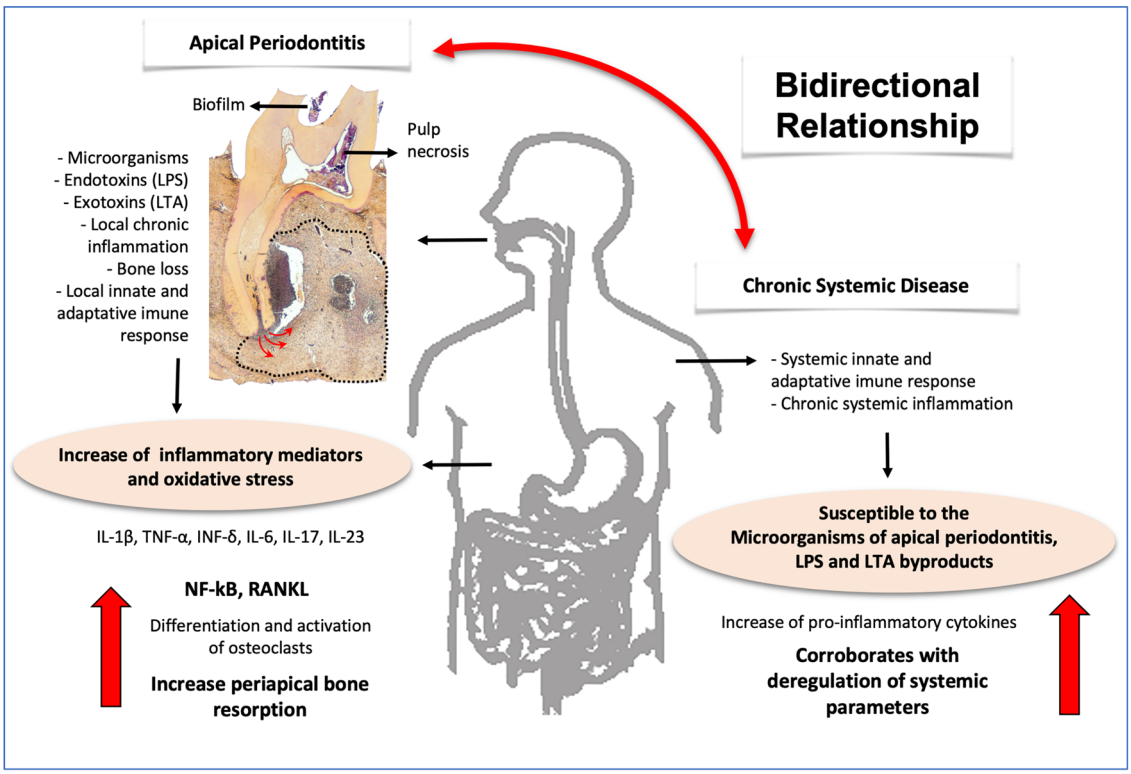

Fig. 1 Potential interrelationship between apical periodontitis and systemic disorder. Systemic diseases do the organism more susceptible to infection increasing microorganisms in apical periodontitis and the local immune response maintaining the inflammatory process and periapical bone resorption. The increase of microorganisms in the periapical lesion favors presence and the action of their byproducts in the bloodstream, capable of triggering an immune response and an increase in pro-inflammatory cytokines that will corroborate the dysregulation of systemic parameters

under normal systemic conditions; (2) evidence of relationship between systemic and periapical tissue pathological condition; (3) risk factors and genetic polymorphisms; (4) systemic conditions and endodontic materials; and (5) influence of endodontic materials on different organs and tissues.

Methodology

This narrative review was performed according to Melis et al. and Aidos et al. [16, 17]. A literature survey was conducted to identify the main articles that sought to explain the various systemic conditions that are related and the endodontic results. The research was carried out in PubMed using the keywords systemic conditions, endodontic infection, apical periodontitis, systemic effects, periapical lesion, periapical radiolucency, root canal filling materials, repairing materials, sealing materials, and endodontic sealers. The eligibility criteria were: complete articles published in the English language, original articles with complete rapid rewiew classification, experimental studies, clinical studies and reviews. Exclusion criteria were given outside of English and unpublished, conference articles, and letters to the editor.

Two reviewers analyzed 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 endodontics.The present studydid not intend to be a systematic review but a narrative review, synthesizing the field of endodontic medicine, providing an updated and relevant overview on the subject. The narrative review was the model chosen because the theme is wide-ranging, heterogeneous data not conducive to meta-analysis. For convenience, the results were presented in topic form and synthesized in tables. The order in which the results were exposed and discussed was given by the number of studies located in each topic.

Results and discussion

Effects of apical periodontitisunder normal systemic conditions

Several studies in the Endodontics have already shown that there can be a bidirectional relationship between oral infections and systemic health [18–20]. However, as this topic has been the subject of controversy and errors in the past with the 'theory of focal infection', it is essential to assess the systemic impacts of AP in healthy individuals.

Studies in healthy populations demonstrate that there is no causal relationship between AP and systemic disorders [21, 22]. However, good oral health has been related to the performance of elite athletes [23]. Although the inflammatory process is a beneficial defense mechanism for the organism, the constant release of these mediators and cells can unbalance other pre-existing inflammatory processes [24].

Thus, there are studies in animal models showing that the presence of AP in rats can cause a decrease in the insulin signal in the blood [25] and in the skeletal muscle [26], increasing insulin resistance in blood [27] and in skeletal muscle [28], as well as in the offspring of rats committed to apical injury [29, 30]. However, these same rats did not show hyperglycemia. In other words, in healthy rats there were alterations in some parameters, such as increased TNF-α, increased insulin resistance, but the rats did not become diabetic.Likewise, in systemically healthy rats with local AP there was an increase in cytokines such as TNF-a, interleukins (IL-6, IL-17 and IL-23) and in cells, such as leukocytes, especially lymphocytes, among other alterations, such as changes in the parameters of oxidative stress, not only in the blood, but also in organs, such as heart, liver, and pancreas [12, 31]. In these studies, the more teeth involved, the more cells and mediators were released. Therefore, the systemic impact was greater, which reinforces a dose–effect relationship [12, 32, 33]. The severity of periapical lesions was also related to greater systemic impact [34], as it has already been revealed that classic endodontic treatment is able to reverse the systemic impact [21, 22, 24].

Both the American Society of Endodontics and the Society of Periodontics have expressed themselves to make it clear that (1) there is a systemic impact of oral infections on systemic health and (2) this systemic impact is resolved with classic endodontic and or periodontal treatment [35, 36]. It is important to emphasize the effectiveness of local treatments.

Evidence of relationship between systemic and periapical tissue pathological condition

Diabetes

Type 1 diabetes is the result of an autoimmune destruction of insulin-producing pancreatic β cells or can be triggered in organisms that have long-standing disease in which the pancreas has few insulin-producing cells and β cells are unable of regeneration [37]. Usually, this type of diabetes occurs in childhood or adolescence, and for this reason it is also called Juvenile Diabetes [38]. Type 2 diabetes, on the other hand, is a chronic disease that can have a genetic influence, but which, in most cases, is related to lifestyle [39]. While in type 1 diabetes the pancreas stops producing insulin [38], in type 2 the signaling between secretion and the action of insulin does not work properly.

Currently, diabetes mellitus is the most studied systemic disorder in relation to AP, but understanding the mechanism between these two diseases with such distinct pathogenesis is still a challenge. Animal studies play an extremely important role, as it is through them that researchers make accurate analyzes, excluding the interference of common bias in clinical studies.

The first study using an animal model to link AP and diabetes was carried out by Kohsaka et al. where greater bone resorption was observed in diabetic rats [40]. Studies carried out by our research group have also confirmed that diabetes accelerates the development and progression of periapical lesions with mixed inflammatory infiltrates of neutrophils and mononuclear cells [13, 15]. Subsequent studies showed an increase in IL-17 in the AP of diabetic rats, suggesting that this cytokine is expressed in the development of periapical injury during diabetes and is capable of stimulating bone resorption in tissues [41, 42].

In another study, we mapped T-lymphocyte signaling in AP in diabetic rats by identifying increased releasing cytokines IL-6, TNFα, IL-17, and IL-23 when compared to control group [11]. We also observed that the bacterial infestation in AP was greater in diabetic animals [11], which confirms the ability of the hyperglycemic condition to suppress the immune response against infections. In this regard, Foaud et al. did important discoveries about the severity of microbial infection associated with type 1 diabetes, showing that mice with diabetes were more susceptible to morbidity and mortality than controls after AP induction [43]. To elucidate this topic, we carried out some studies in animal model and observed that AP associated with periodontal disease increased the level of triglycerides [44] and creatinine [45] in diabetic rats. We found that diabetes caused an increase in the average volume of erythrocytes, as well as in the leukocyte and neutrophil counts [13]. The oral infections had a greater impact on the systemic condition already altered by diabetes, increasing the total number of leukocytes, the number of neutrophils and lymphocytes and glucose concentrations [13].

Other studies showed that association of AP and periodontal disease worsened the deleterious effects of diabetes, affected glycemic conditions and the level of glycosylated hemoglobin (HbA1c) in diabetic rats [15] and increased the mean platelet count and blood glucose level [46], contributing to the loss of body weight and altering the weights of the liver, brain, heart and gonads [47]. Our group also observed that the combination of AP with periodontal disease increased serum levels of IL-17 in diabetic and normoglycemic rats and also the level of neutrophils in diabetic rats [14].

In other studies, we observed that diabetes increased levels of IL-17 in the liver and kidney tissues, and increased production of IL-17 in rat AP [42]. The serum oxidative stress and the antioxidant capacity of the body were also evaluated and we found that diabetes can alter the antioxidant status, increase the concentration of the malonaldehyde oxidative parameter and uric acid and decrease serum albumin levels. In addition, AP can potentiate the effects of diabetes, further reducing albumin levels and further increasing serum uric acid levels [48].

This series of experimental studies supports the hypothesis that AP has a certain influence on the diabetic condition of rats. Also, that the diabetic condition also influences the severity and progression of AP [11, 47]. As observed in the animal studies, clinical studies also show, in most cases, a bidirectional relationship between diabetes mellitus and AP, in relation to prevalence, severity, disease control and response to treatments.

Table 1 summarizes the characteristics of the main findings of clinical studies that assessed the association between endodontic parameters and diabetes [10, 18, 19, 49–57]. In summary, all 12 selected articles included in Table 1 showed at least one type of association between PA and diabetes. Furthermore, three systematic reviews and meta-analysis also confirmed associations between PA and diabetes: Segura-Egea et al. and Gupta et al. showed that diabetes is significantly related to the presence of periapical lesions in teeth that received endodontic treatment [58, 59], and Cabanillas-Balsera et al. showed that the prevalence of teeth with the extracted root canal in diabetic patients was significantly higher [60].

According to the above, the evidence in both human and animal studies indicate the existence of a bidirectional relationship between endodontic infection and diabetes mellitus, and it is important to highlight the difference between the bidirectional association and the causality relationship, that is, it cannot yet be said that there is a cause–effect relationship [61].

Atherosclerosis and cardiovascular diseases

Atherosclerosis is characterized by the formation of atheromas in the internal wall of the main blood vessels. Furthermore, is the underlying disease that leads to the most prevalent cardiovascular diseases (CVD) such as angina, ischemic stroke, acute myocardial infarction, and other cardiovascular events including death. CVD are the main cause of death globally, taking an estimated 17.9 million lives each year [62].

For more than a century, endodontic infections were reported to be linked to angina and endocarditis through metastatic pathways [2, 4, 5]. In the late 1980s, a case–control study revealed that higher scores of the "dental index"—based on the severity of different oral conditions including the number of carious teeth and the number of teeth presenting periapical lesions—was strongly associated with acute

Table 1 Characteristics and main findings of clinical studies evaluating the association between endodontic parameters and diabetes mellitus

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Diabetes outcomes	Main findings and effect estimates (95%CI)	Association endo × DM
Fouad and Burleson (2003) [18]	Retrospective cohort	6034	AP, DM	Periapical X-ray	Data from an electronic patient record	Patients with DM have increased PD in teeth involved endodontically and have a reduced likelihood of success of ET in cases with preoperative AP *P* value = 0.008 for increased PD *P* value = 0.007 for likelihood of success	Confirmed
Segura-Egea et al. (2005) [19]	Retrospective cohort	70	AP, DM	Periapical X-ray	Fasting plasmaglucose and 75-g oral glucose tolerance test	T2DM is significantly associated with an increased prevalence of AP AP ≥ 1OR = 3.2 (1.05–9.44)	Confirmed
López-López et al. (2011) [49]	Retrospective cohort	100	AP, DM	Panoramic X-ray	Diagnosed according to the criteria of The Expert Committee on the Diagnosis and classification of DM	T2DM is significantly associated with an increased prevalence of AP and ET AP ≥ 1OR = 3.9 (1.05–1.40) ET ≥ 1 OR = 2.3 (1.0–5.3)	Confirmed
Marotta et al. (2012) [50]	Cross sectional	90	AP, DM, RCT	Panoramic X-ray	Uninformed	AP was significantly more prevalent in untreated teeth from T2DM *P* value = 0.03 for AP	Confirmed
Sánchez-Domínguez et al. (2015) [54]	Retrospective cohort	83	AP, Glycemic control	Periapical X-ray	HbA1c levels	Worse periapical status correlated significantly with HbA1c levels ≥ 6.5% in type 2 diabetic patients Presence AP in poor control HbA1c group OR = 3.8 (1.1–13.0)	Confirmed
Rudranaik et al. (2016) [55]	Case–control	80	DM	Clinical and radiographic diagnosis	HbA1c levels	T2 DM had larger sized AP when compared to control subjects. AP in patients with poor diabetic control showed failure. The clinical and radiographic healing outcome of single visit endodontic therapy was delayed in DM patients *P* value = 0.02 for sized AP	Confirmed

Table 1 (continued)

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Diabetes outcomes	Main findings and effect estimates (95%CI)	Association endo×DM
Smadi (2017) [52]	Cross sectional	709	AP, DM, Glycemic control	Digital panoramic radiographs	HbA1c levels	Diabetic group had more ET teeth compared with non-diabetic group. Poorly controlled diabetic group had more AP lesions, ET teeth and the AP/ET ratio *P* value = 0.001 for ET and AP	Confirmed
Arya et al. (2017) [10]	Case–control	60	DM	Periapical X-ray	HbA1c levels	DM may have a negative impact on the outcome of endodontic treatment in terms of periapical healing *P* value < 0.05 for periapical healing	Confirmed
Nair et al. (2019) [57]	Cross sectional	60	DM	Clinical examinations, periapical radiographs, and PCR	Blood sugar level and HbA1c levels	Enterococcus faecalis (73.3%) was the predominant bacteria isolated from the root canal in type 2 diabetic patients *P* value = 0.00 for EnterococcusFaecalis	Confirmed
Sisli et al. (2019) [53]	Cross sectional	237	AP, DM	Computed tomography	DM patients who had been followed up in the Endocrine Polyclinic	The prevalence of AP and severe bone destruction in periapical tissues was significantly higher in the DM patients compared with the non-diabetic patients *P* value < 0.05	Confirmed
Limeira et al. (2020) [51]	Cross sectional	150	AP, DM, ET	Panoramic X-ray	Diagnosis of DM based on the criteria established by the American Diabetes Association	ET with AP was more prevalent in individuals with T1DM than in non-diabetic individuals AP number OR = 1.95 (0.88–4.34) ET number OR = 1.58 (0.94–2.67)	Confirmed

Table 1 (continued)

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Diabetes outcomes	Main findings and effect estimates (95%CI)	Association endo × DM
De la Torre-Luna et al. (2020) [56]	Cross sectional	120	DM	Periapical X-ray, PCR	Diagnosis of DM based on the criteria established by the American Diabetes Association	T2DM patients carried C. albicans in their root canals more frequently when having a primary endodontic infection *P* value = 0.02 for C. albicans in DM	Confirmed

AP apical periodontitis, *DM* diabetes mellitus, *ET* endodontic treatment, HbA1c Glycosylatedhemoglobin, *OR* odds ratio, *PD* periodontal disease, *T1DM* diabetes mellitus type 1, *T2DM* diabetes mellitus type 2

myocardial infarction [63]. Recently, investigations on the relationship between endodontic diseases and cardiovascular events are focused on the chronic nature of asymptomatic AP, which may affect an individual for long periods.

The potential biological plausibility linking endodontic diseases and atherosclerotic CVD have been described through three main routes [64]: (a) the occurrence of transitory bacteremia resulting from the infected root canal system [65, 66]; (b) the vascular dissemination of toxins and byproducts from endodontic microorganisms [67]; (c) the low-grade systemic inflammatory response [68, 69] and oxidative stress [70] resulting from the presence of chronic AP. The main pathogenic mechanisms are based on the possible role of endodontic microflora and their toxins in the occurrence of endothelial dysfunction [71], favoring the development of initial atherosclerotic lesions. It is also suggested that oral microorganisms may contribute to the increase in the thickness of atheromatous plaques, since many studies have identified the presence of oral microorganisms within vascular lesions [72, 73]. Finally, it has also been described that oral microflora can contribute to the modulation and maturation of atheroma, facilitating the rupture and consequent vascular thrombosis [74].

Based on the reasonableness of these mechanisms, some animal and several human studies have emerged with the intention to explore the association between endodontic parameters, atherosclerosis and cardiovascular outcomes. Studies using animal models have suggested that the influence of AP on systemic inflammatory parameters is directly related to the number of affected teeth [12, 33], which indicate a possible dose–response effect in the relationship between AP and cardiovascular risk.

One study revealed that AP was related to changes in the aortic arch and myocardium of Wistar rats [75]. However, it should be noted that the number of animals per group was 3, which makes any kind of conclusion on the subject impossible. Using models of hypertension, Martins et al. showed greater differentiation of osteoclasts in vitro, however they did not detect greater periapical lesion in vivo [76].

The interrelationship of atherosclerosis with AP was tested in mice, and no differences were found in the size of the periapical lesion in the presence of atherosclerosis, nor in the degree of atherosclerosis [77]. On the other hand, a recent study conducted by Conti et al. evaluated the bidirectional relationship between AP and atherosclerosis in Wistar rats, showing that AP potentiated the increase in triglyceride levels, and increased the thickness of the carotid artery intima tunica [78]. Furthermore, that study identified that atherosclerosis intensified the inflammatory reaction and increased bone resorption in periapical lesions.The different results reported by Berlin-Broner et al. and Conti et al. should be interpreted as a result of methodological differences related to the animal species used, the time of AP

development, and the method of inducing atherosclerosis [77, 78].

Another study observed that rats with AP presented increases in oxygen species in the heart and the sodium pump Na^+K^+-ATPase; NKA (NKA) activity was increased in this organ [31], suggesting that a cellular electrochemical gradient alteration may be involved in the periapical lesion physiopathology, thus modulating the NKA activity and the endogenous antioxidant defense. The use of animal models for the study of systemic diseases and oral infections has its limitations, and its results should not be directly associated with responses in humans. On the other hand, these studies allow the investigation of the mechanisms involved between these diseases.

The Table 2 summarizes the characteristics and main findings of human clinical studies evaluating the association between endodontic parameters and cardiovascular outcomes [71, 79–99].

Whilst some investigations rejected the association [79, 80, 84, 92, 96] most of the human studies have confirmed the hypothesis of a positive relationship between endodontic variables and different parameters of CVD.

In summary, longitudinal clinical studies demonstrated that AP was significantly associated with a higher risk to develop coronary heart disease among younger individuals (< 40 years old) [81], that endodontic burden in midlife was an independent predictor of cardiovascular events [82]. Some investigations assessed the self-reported history of endodontic treatment (SRHET) as a surrogate of pulpal and periapical diseases, evaluating the relationship between SRHET and cardiovascular outcomes in large samples. In these studies, were observed a 21% increased risk of coronary heart disease in subjects reporting SRHET [85], and significant association between endodontic pathology and CVD and its risk factors, particularly hypertension [80]. In a cohort study [86], was observed that patients with unfinished root canal treatment were associated with a higher risk of hospitalization due to CVD. On the other hand, patients with complete root canal treatment had 84% and 49% reduced risk to develop CVD and cardiovascular related-death, respectively [87].

The strength of the association between endodontic parameters and cardiovascular outcomes varies between studies. Based on the available evidence, it is possible to observe that the risk estimates range from 1.40 [81] to 4- [88] or 5-fold [89] higher risk to present some CVD in subjects with AP, compared to subjects without endodontic disease.

Recent systematic reviews assessed the association between CVD and AP [100–102], including an umbrella review [103]. In conjunction, available data raised by observational studies suggests a moderate to weak association between CVD and AP. Most importantly, a causal relationship cannot be established, considering the lack of prospective interventional studies designed to evaluate the impact of the treatment of endodontic diseases on the risk to the development of CVD. In addition, atherosclerosis, CVD and pulp and periapical diseases share several common risk factors, such as age, socioeconomic status, diet, diabetes, smoking, among others, which challenges the investigation of a causal connection.

Thus, this clinically research topic needs further longitudinal clinical studies using long term follow-up periods in large samples with different sociodemographic, economic and health profiles. Meanwhile, clinicians should be aware that AP may have both local and systemic implications, and the presence of chronic endodontic infection may be considered an additive risk indicator for CVD, especially along with active periodontal disease and other systemic comorbidities.

Hepatic diseases

The liver changes have gained ground in studies associated with oral infections, since the liver is an organ responsible for the hemostasis of the entire organism and the diseases that affect it are among the most prevalent in the world population [104]. Studies in humans and animals have detected the presence of oral microorganisms in the liver of non-alcoholic liver steatosis patients, showing that oral diseases act as a risk factor for the pathogenesis and progression of liver disease [105, 106].

An animal model study showed that AP elevated the levels of C-reactive protein, IL-2, and IL-6 in blood serum, causing irreversible changes in the liver [75]. However, the number of animals per group precludes any conclusions about the finding. On the other hand, recently, Cantiga-Silva et al. investigated the effects of liver fibrosis on pro-inflammatory mediators and on periapical bone resorption of AP in rats [107]. The results showed a more intense inflammatory infiltrate, a greater amount of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and increased periapical bone resorption in the presence of hepatic fibrosis [107].

Regarding human studies, few studies have addressed this type of relationship and Table 3 summarizes the characteristics and main findings of clinical studies that assessed the association between endodontic parameters and hepatic disease [108–110], and other systemic diseases and conditions.

In summary, in a clinical study it was possible to verify an association between the significantly higher prevalence of radiographic periapical lesions and the lower frequency of filled root canals in liver transplant candidates compared to healthy control subjects [108]. It was also observed presence of AP in one or more teeth in 46% of the patients with cirrhosis and association of AP with higher prevalence of complications related to cirrhosis, such as ascites, hepatic

Table 2 Characteristics and main findings of clinical studies evaluating the association between endodontic parameters and cardiovascular outcomes

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Cardiovascular outcomes	Main findings and effect estimates (95%CI)	Association endo × CVD
Frisk et al. (2003) [79]	Cross sectional	1056	AP, ET	Panoramic X-ray	CHD (angina, AMI)	No association between AP or ET and CHD among woman PA > 2 OR = 0.95 (0.21–4.37) ET > 2 OR = 1.52 (0.62–3.77)	Rejected
Joshipura et al. (2006) [83]	Retrospective cohort	34,683	ET	SRHET	AMI, CV-death	Modest association between ET (surrogate of pulpal inflammation) and CHD ET ≥ 1 RR = 1.21 (1.05–1.40)	Confirmed
Caplan et al. (2006) [81]	Retrospective cohort	708	AP, ET	Periapical X-ray	Angina, AMI, ICC	Significant association between incident AP and time to CHD in men ≤ 40-year old AP ≥ 3/years HR = 1.40 (1.10–1.80)	Confirmed
Caplan et al. (2009) [85]	Cross sectional	6.651	ET	SRHET	CHD	Significant association between SRHET and CHD SRHET ≥ 2 OR = 1.62 (1.04–2.53)	Confirmed
Willershausen et al. (2009) [98]	Case–control	250	AP, ET	Panoramic and periapical X-ray	AMI	Significant association between chronic oral infections and AMI *P* values = 0.01 for AP and ET Effect estimates not reported	Confirmed
Oikarinen et al. (2009) [94]	Case–control	88	AP, ET, dental index	Panoramic X-ray	CAD (Angina, AMI)	Significant association between periodontitis, AP and CAD *P* value = 0.008 for AP Effect estimates not reported	Confirmed
Segura-Egea et al. (2010) [96]	Case–control	91	AP, ET	Periapical X-ray	Hypertension	No association between APor ET and hypertension AP ≥ 1 OR = 1.94 (0.78–4.81) ET ≥ 1 OR = 1.27 (0.55–2.93)	Rejected

Table 2 (continued)

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Cardiovascular outcomes	Main findings and effect estimates (95%CI)	Association endo × CVD
Cotti et al. (2011) [71]	Case–control	40	AP	Panoramic and periapical X-ray	SICI	AP increased the serum markers of inflammation and reduced the EFR *P* values < 0.01 for EFR Effect estimates not reported	Confirmed
Pasqualini et al. (2012) [88]	Case–control	100	AP	Periapical X-ray	CHD (Angina, AMI)	Significant association between chronic oral diseases and increased risk of CHD AP ≥ 1 OR = 4.37 (1.69–11.28)	Confirmed
Glodny et al. (2013) [92]	Cross sectional	292	Caries, AP	CT	Aortic atherosclerosis	Significant association between caries and atherosclerotic burden. AP was not associated with atherosclerosis after adjustment Caries OR = 5.11 (2.44–10.71) AP *P* > 0.05; OR not reported	Rejected
Willershausen et al. (2014) [99]	Case–control	497	AP, dental index	Panoramic and periapical X-ray	AMI	Significant association between tooth loss, AP and AMI Tooth loss OR = 1.21 (1.14–1.28) AP ≥ 1 OR = 1.54 (1.10–2.16)	Confirmed
Petersen et al. (2014) [95]	Cross sectional	531	AP, ET	CT	Aortic atherosclerosis	Significant association between AP and atherosclerosis. AP in teeth with ET was not associated with atherosclerosis AP ≥ 1 in teeth without ET: OR = 1.61 (1.39–1.86)	Confirmed
Costa et al. (2014) [91]	Cross sectional	103	AP	Periapical X-ray	CAD	Significant association between AP and CAD AP ≥ 1 OR = 2.79 (1.1–7.3)	Confirmed

Table 2 (continued)

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Cardiovascular outcomes	Main findings and effect estimates (95%CI)	Association endo × CVD
Lin et al. (2015) [86]	Retrospective cohort	283,590	Unfinished ET	Health records	Hospitalization due to CVD	Patients with unfinished ET were associated with a higher risk of CVD hospitalization Unfinished ET ≥ 3 HR = 3.61 (2.36–5.51)	Confirmed
Gomes et al. (2016) [82]	Retrospective cohort	278	AP, ET, EB, OIB	Panoramic X-ray	Angina, AMI, CV-death	EB in midlife was an independent predictor of CVE EB ≥ 3 RR = 1.77 (1.04–3.02)	Confirmed
An et al. (2016) [89]	Case–control	364	AP	Periapical X-ray	CVD, Hypercholesterolemia, Hypertension	Significant association between AP and CVD, with subjects with AP presenting a fivefold higher chance than subjects without AP AP ≥ 1 OR = 5.3 (1.5–18.4)	Confirmed
Liljestrand et al. (2016) [93]	Cross sectional	508	AP	Panoramic X-ray	CAD, ACS	Significant and independent association between AP, CAD and ACS AP ≥ 1 OR = 2.46 (1.09–5.54)	Confirmed
Virtanen et al. (2017) [97]	Cross sectional	120	AP, dental index	Periapical X-ray	CVD	Significant and independent association between AP and CVD AP ≥ 1 OR = 3.83 (1.18–12.40)	Confirmed
Meurman et al. (2017) [87]	Case–control	473	ET	Panoramic X-ray	CAD, CV-death	ET significantly reduced the risk of CAD and CV-death ET ≥ 1OR = 0.16 (0.09–0.28) for CAD ET ≥ 1 HR = 0.51 (0.27–0.97) for CV-death	Confirmed
Chauhan et al. (2019) [90]	Case–control	120	AP	Panoramic X-ray	FMD, c-IMT	Individuals with AP showed significantly worse FMD% (4.9% vs 9.7%) and increased c-IMT (0.64 vs 0.54 mm) than individuals without AP *P* value < 0.05 for FMD and c-IMT Effect estimates not reported	Confirmed

Table 2 (continued)

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Cardiovascular outcomes	Main findings and effect estimates (95%CI)	Association endo × CVD
Messing et al. (2019) [80]	Retrospective cohort	666,768	AP, ET, SRHET	Electronic health records	CVDs, Hypertension	Significant associations between endodontic pathology and CVDs and its risk factors, particularly hypertension *P* value < 0.001 for all CVDs combined Effect estimates not reported	Confirmed
Messing et al. (2019) [80]	Case–control	384	AP, ET, SRHET	Electronic health records	Genetic polimorphism	A trend of a positive association (non-significant) was found between AP and KCNK3 gene, suggesting that common genetic variations may underlie both CVD and endodontic diseases *P* value = 0.05 for KCNK3 Effect estimates not reported	Rejected
Cowan et al. (2020) [84]	Retrospective cohort	6638	ET	SRHET	CHD, stroke, heart failure, VTE	SRHET was not associated with risk to CVDs ET ≥ 1 HR = 1.16 (0.87–1.44)—CHD ET ≥ 1 HR = 0.77 (0.55–1.09)—stroke ET ≥ 1 HR = 1.00 (0.81–1.24)—heart failure ET ≥ 1 HR = 0.98 (0.67–1.43)—VTE	Rejected

AP apical periodontitis, *CT* computed tomography, *ET* endodontic treatment, *EB* endodontic burden, *OIB* oral inflammatory burden, *SRHET* self-reported history of endodontic treatment, *ACS* acute coronary syndrome, *AMI* acute myocardial infarction, *ICC* ischemic chronic cardiopathy, *CV-death* cardiovascular-related death, *CVD* cardiovascular disease, *CAD* coronary artery disease, *CHD* coronary heart disease, *SICI* subclinical initial cardiovascular injury, *EFR* endothelial flow reserve, *FMD* flow-mediated dilatation, *c-IMT* carotid intima-media thickness, *OR* odds ratio, *PR* prevalence ratio, *oRR* relative risk, *HR* hazard ratio, *VTE* venous thromboembolism

Table 3 Characteristics and main findings of clinical studies evaluating the association between endodontic parameters and systemic outcomes of hepatic and other systemic disorders or condition

Systemic condition	Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Systemic outcomes	Main findings and effect estimates (95% CI)	Association
Liver disease	Castellanos-Cosano et al. (2013) [108]	Cross sectional	84	AP, AT	Panoramic X-ray	liver transplantation candidates	Significant association between AP or and liver transplantation candidates AP ≥ 1 OR = 3.7 (1.4–9.5) ET ≥ 1 OR = 0.14	Confirmed
Liver disease	Grønkjær et al. (2016) [109]	Cross sectional	110	AP	Panoramic X-ray	Cirrhosis	Patients with AP showed significantly increased of the cirrhosis (46% vs 27%) than individuals without AP AP ≥ 1; *P* value = 0.05	Confirmed
Liver disease	Braga Diniz et al. (2020) [110]	Controlled Clinical Trial	22	PN	X-ray and PST	CLD	No significant differences between CLD and levels of the IL-1b, IL-10, IL-6 and the chemokines MCP-1/CCL-2 and VEGF in PN *P* value > 0.05	Rejected
Bone disease	López-López et al. (2015) [111]	Cross sectional	75	AP	Panoramic X-ray	BMD	Significant BMD was associated with a higher frequency AP *P* value = 0.05; AP ≥ 1OR = 1.9 (1.0–3.8)	Confirmed

Table 3 (continued)

Systemic condition	Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Systemic outcomes	Main findings and effect estimates (95% CI)	Association
Kidney disease	Khalighinejad et al. (2017) [112]	Cross-sectional	80	AP, ET	Panoramic and periapical X-ray	ESRD	Significant association between AP, and ESRD. No significant differences between ET and ESRD AP ≥ 1 OR = 3.95 (1.54–6.32) ET ≥ 1 OR = 2.54 (0.9–5.32) AP was significantly associated with the urea serum level in ESRD $P < 0.05$, β coefficient = 4.35	Confirmed
Pregnancy	Harjunmaa et al. (2015) [113]	Cross sectional	1024	Caries, AP	Panoramic X-ray	IUGR, PTB	Significant association between IUGR and PTB with AP, but no with Caries PTB and AP = *P* value = 0.014 AP ≥ 1 RR = − 0.4 (− 0.8 to − 0.1) IUGR and AP = *P* value = 0.002 AP ≥ 1 RR = − 0.5 (− 0.9 to − 0.2)	Confirmed
Pregnancy	Khalighinejad et al. (2017) [114]	Case–control	100	AP, ET	Periapical X-ray	Preeclampsia	Significant association between preeclampsia and AP or ET *P* value = 0.002 AP ≥ 1 OR = 2.4 (1.1–5.62) *P* value = 0.001 AP ≥ 1 OR = 0.24 (0.1–0.58)	Confirmed

Table 3 (continued)

Systemic condition	Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Systemic outcomes	Main findings and effect estimates (95% CI)	Association
Bowel disease	Piras et al. (2017) [115]	Cross sectional	110	AP	Periapical X-ray	Inflammatory bowel disease	The number of teeth with AP was significantly higher in female patients with inflammatory bowel disease than controls AP ≥ 1; *P* value = 0.42	Confirmed
Bowel disease	Poyato-Borrego et al. (2020) [116]	Case–Control	108	AP, ET	Panoramic X-ray	Inflammatory bowel disease	The number of teeth and ET of the patients with inflammatory bowel disease had more AP than control *P* value = 0.0048 AP ≥ 1 OR 5.7 (1.7–19.1)	confirmed
Bowel disease	Poyato-Borrego et al. (2021) [117]	Cross sectional	54	AP, ET	Panoramic X-ray	Ulcerative colitis and Crohn's disease	Patients with inflammatory bowel disease have higher prevalence of apical periodontitis *P* value = 0.03 AP = OR 2.71 (1.09–6.73)	confirmed
Hematological disease	Castellanos-Cosano et al. (2013) [118]	Cross sectional	116	AP, ET	Panoramic X-ray	ICD	Significant association between AP, and ICD. No significant differences between ET and ICD AP ≥ 1 OR = 2.20 (2.4–22.6) ET ≥ 1 OR = 0.28 (0.13–0.60)	Confirmed
Hematological disease	Ferreira et al. (2015) [119]	Controlled Clinical Trial	24	PN	Periapical X-ray, clinical analysis, PST	SCA	Significant proinflammatory ability to express IL-1, TNF-a, and IL-17A in PN with SCA compared non SCA P value < .05	Confirmed

Table 3 (continued)

Systemic condition	Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Systemic outcomes	Main findings and effect estimates (95% CI)	Association
Hematological disease	Costa et al. (2013) [120]	Retrospective, Prospective and cohort	359	PN	Pulse oximetry, cold thermal test	SCA	Significant association between SCA and PN *P* values < 0.001 PA ≥ 1 RR = 8.33 (4.44–15.6)	Confirmed
Physical fitness	Hope et al. (2017) [121]	Cross sectional	112	AP, ET, EB	Periapical X-ray, clinical analysis	PFT	No significant association betweenAP, RCT and EB with PFT—*P* > 0.05 Higher levels of EB ≥ 3 in periodontal patients—was independently associated withpoor PF OIB = EB ≥ 3 andAL ≥ 4OR = 0.19 (0.04–0.87)	Confirmed

AP apical periodontitis, *ET* endodontic treatment, *CLD* chronic liver disease, *PN* pulp necrosis, *BMD* bone mineral density, *ESRD* end-stage kidney disease, *IUGR* intrauterine growth restriction, *PTB* preterm birth, *ICD* inherited coagulation disorders,*PST* pulp sensibility tests, *SCA* sickle cell anemia, *IBD* inflammatory bowel disease, *EB* endodontic burden, *OR* odds ratio, *RR* relative risk

encephalopathy and/or variceal bleeding [109]. In another study, liver impairment did not compromise the periapical immune response [110]. Despite these findings, the available studies on oral infections do not allow us to establish a cause–effect relationship between AP and liver disease, as well as to substantiate the biological pathways involved in the interrelation between these diseases.

Other systemic diseases and conditions

The advancement in endodontic medicine has arouse researchers to study less common systemic changes, but no less important from a systemic and immunological point of view, such as kidney diseases, diseases of bone metabolism, hematological disorders and physical fitness, with the potential to worsen in the presence of oral infections. Table 3 summarizes the characteristics and main findings of clinical studies that assessed the association between endodontic parameters and other systemic diseases [111–121].

In a clinical study, an association was observed between the presence of PA with osteoporosis and osteopenia [111]. In an animal model, two studies demonstrated a more intense inflammatory response, greater expression of RANKL, greater periapical lesion and greater number of positive cells for tartrate resistant acid phosphatase (TRAP) in rats with osteoporosis [122, 123]. On the other hand, these changes were reversed with treatment with Raloxifene [122, 123]. Patients with kidney disease may also have a greater number of periapical lesions, as well as a greater prevalence of periapical lesions in endodontically treated teeth [112].

Some studies carried out in humans and animals have also shown that endodontic infections in pregnant women may be associated with pre-eclampsia, premature birth or intrauterine growth restriction, in addition to brain injuries in the offspring offspring [113, 114, 124]. Our research group observed that maternal AP promoted insulin resistance in its adult offspring, impaired the initial stages of insulin signaling, significantly increased plasma concentrations of insulin and TNF-a, and exerted an influence on the inflammatory pathways of muscle and adipose tissue [29]. These results demonstrate that maternal AP is associated with insulin resistance and promotes important changes in the signaling and inflammation pathways in the adult life of their offspring, reinforcing the importance that maintaining maternal oral health has on the overall health of the offspring.

A study indicated that women with inflammatory bowel diseases showed higher prevalence of radiolucent periapical lesions and larger perapical lesions than healthy patients [115]. An age- and gender-matched case–control study reported that patients with inflammatory bowel diseases have radiolucent periapical lesions five times more likely than healthy controls [116]. The type of inflammatory bowel disease is not decisive, because the prevalence of radiographically detectable periapical lesions or the prevalence of root canal treatment in both ulcerative colitis and Crohn's disease patients were similar [117].

Hematological diseases, such as bleeding disorders and anemia, have also been investigated in relation to AP. The prevalence of periapical lesions and root canal treatment inpatients with inherited coagulation disorders, such as of hemophilia A, hemophilia B or von Willebrand's disease, was investigated in a cross sectional study [118]. Patients with inherited coagulation disorders showed twice the prevalence of AP, but lower frequency of root canal treatment. The relationship between sickle cell anemia and endodontic infection was also analyzed [119]. Pulp necrosis in clinically intact permanent teeth can be seen in patients with this systemic change [120], who also have an increased susceptibility to infections [125]. It was shown that the expression of messenger RNA for Interferon-γ, TNF-α and IL-1β was significantly higher in the periapical interstitial fluid of patients with sickle cell anemia and periapical injury when compared to control patients [119].

The association between chronic oral inflammatory burden and physical fitness was also investigated in humans. A cross-sectional observational study revealed there was no direct association between the presence of AP and endodontic treatment with the physical performance [121]. However, multivariate regression analysis revealed that individuals presenting both endodontic and periodontal diseases had 81% lower chance of reaching high scores in the physical fitness test compared to individuals with healthy oral parameters [121].

The findings of the studies affirm the bidirectional relationship between infections of endodontic originand systemic diseases. The diagram in Fig. 1 shows how it can occur. Although more studies should be carried out to better understand mechanisms of these interactions, it is clear the importance of eradicating foci of infections from the oral cavity for the benefit of the patient, improving the quality of life not only related to the oral health conditions, but also the systemic health of these patients.

Risk factors and genetic polymorphisms

Smoking habits

Tobacco smoking is a well-established risk factor for systemic and oral health, increasing the risk of caries [126] and periodontal disease [127]. Consequently, periapical bone destruction could be greater in smokers, altering periapical repair after root canal treatment, increasing the number and/or size of periapical lesions [20]. Table 4 summarizes the characteristics and main findings of clinical studies that assessed the association between endodontic parameters and smoking habits [128–140].

Table 4 Characteristics and main findings ofclinical studies evaluating the association between endodontic parameters and smoking habits

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Systemic outcomes	Main findings and effect estimates (95% CI)	Association
Segura-Egea et al. (2008) [128]	Cross sectional	180	AP, ET	Periapical X-ray	Smoking	Significant association between smoking and AP or ET AP ≥ 1 OR = 1.5 (1.1–2.1) ET ≥ 1 OR = 1.7 (1.0–2.6)	Confirmed
Segura-Egea et al. (2011) [129]	Cross sectional	100	AP, ET	Periapical X-ray	Smoke, Hypertension	Significant association between smoking + hypertension and AP or ET AP ≥ 1 OR = 3.3 (2.0–5.4) ET ≥ 1 OR = 2.9 (1.6–5.5)	Confirmed
Kirkevang and Wenzel (2003) [130]	Cross sectional	613	AP	Periapical X-ray	Smoking	Association between smoking and AP *P* value < 0.05 OR = 1.64 (1.00–2.84)	Confirmed
Krall et al. (2006) [131]	Closed-panel prospective study	811	AP, ET	Periapical X-ray	Smoking	Association between smoking and AP HR = 1.9 (1.4–2.6)	Confirmed
Doyle et al. (2007) [132]	Restropective	196	ET	clinical and radiographic	Smoking	Smokers had fewer successes and more failures *P* value = 0.001	Confirmed
Aleksejuniene et al. (2000) [133]	Cross sectional	147	AP	X-ray, clinical analysis	Smoking	Association between smoking and AP Variable B—*P* = 0.05 Variable C—*P* = 0.008	Confirmed
Kirkevang et al. (2007) [134]	Cross sectional	473	AP	Periapical X-ray	Smoking	Smoking was a statistically significant risk factor when associated with AP OR 1.9 (1.3–2.8)	Confirmed
López-López et al. (2012) [135]	Restropective case–control	158	AP	Panoramic X-ray	Smoking	Association between smoking and AP *P* value = 0.000 AP ≥ 1 OR = 32.4 (11.7–89.8)	Confirmed
Oginni et al. (2015) [136]	Cross sectional	285	AP	Periapical X-ray	Smoking	Smoking was statistically significant risk factors for developing AP OR = 3.82 (2.17–6.75)	Confirmed

Table 4 (continued)

Study/year	Study design	*N*	Exposure variables	Diagnostic methods	Systemic outcomes	Main findings and effect estimates (95% CI)	Association
PersikBukmir et al. (2019) [137]	Cross sectional	599	AP	Periapical X-ray	Smoking	Smoking habit on daily basis increase AP *P* value < 0.001 RC = 0.041	Confirmed
Bergström et al. (2004) [138]	Cross sectional	247	AP, ET	Periapical X-ray	Smoking	The differences between smoking AP/ET groups were not statistically significant (prevalence and severity) Mean de AP per patient Current smokers = 1.9 (6%) Former smokers = 1.5 (4%) Non-smokers = 1.0 (3%) AP *P* value > 0.05	Rejected
Frisk and Hakerberg (2006) [139]	Cross sectional	981	AP	Panoramic X-ray	Smoking	No association between smoking and AP *P* value > 0.05 OR = 1.35 (0.91–2.02)	Rejected
Rodriguez et al. (2013) [140]	Cohort	161	AP	X-ray, clinical analysis	Smoking	Quality of root canal filling cigarettesmoking was not associated with apical periodontitis incurrent female and male smokers with < 10 or ≥ 10 pack years *P* value > 0.05	Rejected

AP apical periodontitis, *ET* endodontic treatment, *PST* pulp sensibility tests, *RC* regression coefficient, *OR* odds ratio, *HR* hazard ratio

The scientific evidence relating smoking habits and AP or root canal treatment is conflicting [20, 141, 142]. Although some studies have found no association between smoking and the prevalence of AP [128, 138–140], several other studies have reported significant association between smoking and the prevalence of AP [128–137]. Two retrospective studies have found that RCT in smokers had fewer successes and more failures than in non-smoker patients [140, 143]. Furthermore, two recent systematic reviews with meta-analysis have found significant association between smoking and higher frequency of periapical lesions in endodontically treated teeth [144], and higher frequency of extraction of root-filled teeth [145].

Alcoholism

Smoking habits and excessive alcohol consumption are the main causes of preventable death in the world [146, 147]. Recently, a study evaluated the influence of alcohol associated with nicotine consumption on AP in rats [148]. The result showed intense inflammatory infiltrate and greatest periapical lesion in this association.

The relationship between alcoholism and periapical lesions of endodontic origin was also investigated by our research group in three animal model studies [149–151]. In the first, rats with AP and subjected to chronic alcohol consumption (20% alcoholic solution) showed periapical lesions

with more severe inflammatory infiltrate, and greater osteoclast activity [149]. Another study showed that at higher concentrations (15 and 20%) there was greater severity of AP, exacerbating the markers of inflammation and bone resorption [150]. The third study showed that chronic alcohol consumption increased serum phosphorus and decreased bone density in the periapical region, favoring the development of AP [151].

Although some experimental studies indicate a possible association between chronic alcohol consumption and AP, no clinical studies were found regarding this relationship.

Genetic polymorphism

AP and systemic diseases share risk factors and biological response mechanisms, both of which are subjected to genetic predisposition. Similarly, genetic polymorphism can also explain some of the associations between endodontic disease and systemic pathologies. Genetic polymorphisms result in altered gene expression and functional variations of the encoded molecules. Individuals with specific genotypes could be more susceptible to disease or could present an increase in disease severity. Polymorphisms of genes encoding for cytokines, enzymes, transcriptional factors, or other molecules implicated in immune and reparative responses, are associated with systemic diseases, such as cardiovascular disease or diabetes.

On the other hand, the outcome of root canal treatment is related closely to the host immune and reparative responses. Consequently, the same genetic polymorphism that increases a predisposition to systemic diseases could, at the same time, increase susceptibility to AP, or delay periapical repair, causing persistent AP. For example, polymorphisms in IL-1B gene are associated with AP [152], but also with the risk of myocardial infarction or stroke [153]. Likewise, single nucleotide polymorphism in KCNK3, a gene known to be involved in increased susceptibility to hypertension, is also associated with AP [79]. The existence of genetic polymorphisms involved, at the same time, in the etiology of a systemic disease and AP, could explain the association between both diseases observed in epidemiological studies.

Systemic conditions and endodontic materials

Endodontic materials

The application of dental materials in clinical is related to the therapy to be employed. The materials available are commonly classified according to their specific use in endodontics: pulp capping materials, regenerative endodontic materials, root canal sealers, apical plug, perforation repair cements, root-end filling materials and perforation repair cements [154]. The interaction between the biomaterial and the tissues can be complex, as it depends on the composition of the material, on the intensity of the elicited immune response and also on the influence of systemic disorders that may be present [32].

Impact of systemic disorders on biocompatibility of endodontic materials

Biocompatibility can be assessed by the inflammation induced in the tissues where the material was inserted [155–159]. However, the systemic disorders can alter the biocompatibility of these materials [32].

Some studies analyzed the biocompatibility of materials in the subcutaneous tissueof hypertensive rats. In these studies, hypertensive condition exacerbated the inflammatory response induced by white and gray MTA (Angelus Industry Ontological Products, Londrina, PR, Brazil) [159], Biodentine (Septodont Inc., Saint-Maur-des-Fosses, France) and the MTA Repair High-plasticity (MTA HP; Angelus) [160].

A study evaluated whether hyperglycemia would be able to influence the process of repair in exposed pulps capped with MTA [161]. It was observed that 54% of diabetic animals showed no inflammation compared to 92% of non-diabetic animals. In another study, similar results were observed for the calcium enriched mixture (CEM) cement [162]. In contrast, studies that evaluated the biocompatibility of Sealapex (Sybron Endo, Glendora, USA), a calcium hydroxide-based endodontic sealer, and MTA Fillapex (Angelus), an endodontic sealer containing MTA showed no significant difference between diabetic and normoglycemic animals [163, 164].

Other study evaluated whether the hyperglycemia would to influence the in vitro and in vivo biocompatibility of gray (GMTA) and white (WMTA) MTA [165]. Under high glucose rates conditions, treatment of fibroblasts cells with GMTA demonstrated reduced cell proliferation and higher production of interleukin-6. In the in vivo study, the hyperglycemic state did not alter the biocompatibility of MTA.

Bleaching materials, such as hydrogen peroxide (H_2O_2), are widely indicated for bleaching of dental structures [166–168]. As other materials, bleaching agents interact with tissue and induce inflammatory response. In particular, in the case of bleaching vital teeth, these substances may cause an exacerbated inflammatory response and possible necrosis in dental pulp [169] probably due to the release of reactive oxygen species (ROS) by the material during application [170].

Still regarding the hyperglycemic condition, studies involving dental bleaching have also been carried out. Greater pulp inflammation and areas of necrosis were observed in hyperglycemic animals after the use of bleaching agent [171], as well as greater immunostaining of pro-inflammatory cytokines [172].

Impact of systemic disorders on biomineralization of endodontic materials

Studies have been carried out to verify the influence of systemic conditions on the biomineralization capacity of materials [160, 161]. One study demonstrated that diabetes negatively influences hard bridge formation after pulp capping with MTA in rats [161]. On the other hand, another study used MTA and CEM found no difference in the dentin bridge formed in healthy and diabetic animals [162]. Other studies using different methodology also did not observe the influence of diabetes on the biomineralization capacity of Sealapex and MTA Fillapex sealers [163, 164].

In a recent study it was observed that that GMTA was able to inhibit the proliferation rate and IL-6 production under high glucose concentration in vitro. In addiction, cytokines production and inflammatory response were not upregulated in hyperglycemic animals; however, a decrease in the calcium deposition was observed in presence of WMTA, suggesting a delay in the mineralization process [165]. These results are supported by a previous study that found in diabetic conditions an inhibitory effect on MTA-induced differentiation of OCN- and OPN-positive cells was detected [173].

In the condition of hypertension, it was observed that the presence of the calcite crystals in the initial periods of analysis was lower in the hypertensive condition when compared to healthy animals [159]. In another study, MTA induced less immunolabelling of RUNX-2, OPN, and OCN under hypertensive conditions [174]. The negative influence of hypertension in the biomineralization of MTA and Biodentine was confirmed in other study [160].

A recent study showed that hypertensive animals show changes in calcium absorption in the gut and loss of this ion in the urine, which can lead to undesirable conditions in the bones [175]. In addition, there was an increase in osteoplastic cells associated with a decrease in osteoblastic cells in these animals, indicating an interference in the bone tissue remodeling process [175]. The same occurs in diabetes, as the literature shows decreased mineralization, lower bone apposition rate, and decreased bone formation [176]. These data can help explain the results found in the studies previously described.

Influence of endodontic materials on different organs and tissues

When a biomaterial is implanted in a living organism, a series of inflammatory reactions can be triggered, such as an immune response, foreign body reaction—which will isolate the material with connective tissue, and possible infection [177–179]. The blood contact with the material occurs, and depending of composition of material, particle size, solubility, amount of material, its ionic dissolution and setting time [177, 180, 181], can induce toxicity, embolization of particles of the material, and to increase amount of chemical compounds from the material in other parts of the body [182, 183]. Thus, the ISO 10993-1 specification delimits that systemic toxicity of all biomaterials that contacted blood must be assessed.

Potential toxic compounds of endodontic materials

Heavy ions present have been identified in organs after use of the MTA and other biomaterials [184, 185]. The changes in the blood were also investigated [173, 186].

Among the metals evaluated are chromium, arsenic, lead, and others. Some chromium compounds can enter the cell and form highly reactive chromium, or causing morphological changes [187]. At the same time, molecular oxygen is converted, leading to oxidative stress and DNA damage [181]. Arsenic salts can be absorbed by all mucous membranes, leave the bloodstream quickly and are deposited in tissues and organs [188], dependent on dose used.

Some studies showed low levels of arsenic released by MTA, MTA-based materials and Portland cement, and the highest values were well below toxic levels [189, 190]. On the other hand, one study identified heavy metals in Portland cement, ProRoot MTA (Tulsa Dental, Johnson City, TN, USA) and MTA-Angelus (Angelus), with high levels of chromium compared to arsenic and lead [191]. Despite these observations, other studies showed that only Portland cement was reported to have high levels of leached arsenic [191, 192].

Other heavy metals have also been investigated, such as, cadmium, copper, iron, manganese, nickel and zinc. Both ProRoot MTA and Ortho MTA (BioMTA, Seoul, Republic of Korea) had low levels of these metals (except zinc in Ortho MTA), within those allowed for use in the human body [193]. The same was observed in relation to arsenic and lead in MTA-Angelus, Micro Mega MTA (Besançon, CEDEX, France) and BioAggregate (Innovative Bioceramix, Vancouver, Canada) [193]. The trace of aluminum was observed only in the BioAggregate material [193]. The greatest release of ions from the materials occurs before of setting and a slower release of metal ions can remain for days [191, 192].

We sought to investigate the possible systemic toxic effects that these materials could promote in various organs and in blood.

Influence on organs and blood changes

Tubes filled with epoxy resin-based cement (AH-26; Dentsply Maillefer, Ballaigues, Switzerland), zinc–eugenol oxide cement (Roth 811; Roth's International, Chicago, IL, USA),

and cements containing calcium hydroxide (Calciobiotic Root Canal Sealer, CRCS; Hygienic Corp., Akron, OH, and Sealapex; Kerr Division, Sybron Corp., Romulus, MI) were implanted on the dorsum of rats [184]. AH-26 had an increase in calcium in the uterus and brain, which also showed an increase of zinc. CRCS sealer led to increased levels of zinc in the brain and uterus. Roth 811 sealer resulted in an increase of zinc in the liver. Other study also evaluated Roth 811 and revelated that there was alterated concentrations of the zinc, calcium, and copper in the liver, heart, kidney, and brain [194]. This can lead to renal or neurological injuries [195].

A histological study analyzed the livers and kidneys of rats after subcutaneous implantation of the ProRoot-MTA and BioAggregate. There was significant inflammation in these organs, mainly with ProRoot-MTA, and an increase in serum levels of the alanine aminotransferase and AST markers (liver function) [182].

It was also investigated whether MTA (Angelus), MTA Fillapex, and Theracal LC (Bisco Inc., Schamburg, IL, US) could influence the levels of aluminum in the plasma and in the liver of rats, when implanted in alveolus [185]. The increase in plasma aluminum levels was mainly present with MTA and MTA Fillapex. However, the materials did not alter the levels of aluminum in the liver [185]. The authors evaluated aluminum levels in the brain and oxidative stress parameters (thiobarbituric acid reactive substances [TBARS], catalase activities [CAT], superoxide dismutase [SOD] and glutathione peroxidase [GPx]) in rats [196]. At 7 days, aluminum levels in the brain were elevated with all materials. Only MTA allowed aluminum levels to decrease over time. There was a significant increase in TBARS in the brain of rats in the presence of all materials, decreasing later. Only at 7 days, CAT activity was higher in the MTA, SOD in the MTA and MTA Fillapex, and GPx in the MTA and Theracal LC groups. The materials had the potential to induce oxidative stress in the brain. However, no direct relationship was identified between aluminum levels and the oxidative stress, which may indicate the action of other metal ions [196]. Later, the authors observed that the oxidative stress was increased in the liver, but in a transient manner [181].

Other study evaluated the effects of Micro Mega MTA, BioAggregate, and Biodentine when implanted on the dorsum of rats [183]. At 45 days, the kidneys had levels of chromium and magnesium, the brain had levels of chromium, and the livers, magnesium. However, the values were still below those considered toxic.

The EndoBinder material (Federal University of São Carlos)—same indications of the MTA, also was evaluated [197]. Areas of microvesicular steatosis were observed on livers [182]. The kidneys also had degenerated glomeruli. However, the most significant results were found in the MTA group, which also resulted in increased liver functions [197].

The levels of calcium, phosphorus and alkaline phosphatase were assessed in the blood of normoglycemic and diabetic rats, which received the implantation of gray and white MTA [173]. Calcium levels were elevated only in normoglycemic rats. Phosphorus levels were not influenced by the materials, except at 7 days with white MTA group of diabetic rats, which had a reduction. An increase in alkaline phosphatase was present at 7 days in the white MTA group of normoglycemic rats. In the comparison between normoglycemic and diabetic animals, differences were observed when evaluating the levels of alkaline phosphatase, which were elevated in diabetics with all materials. However, these are changes that were related to diabetes.

A study implanted roots of teeth with the filled canals with Endomethasone N sealer, in the subcutaneous tissue of mice [186]. This endodontic sealer has hydrocortisone in its composition, and the authors' objective was to quantify the presence of hydrocortisone in organs and tissues. The tissue was collected around the implanted dental apex (simulating the periapical tissues), of the liver, spleen and kidneys. The authors observed radioactive hydrocortisone in the periapical tissues at 2 h, which reduced over time. Radioactivity was also detected in the blood, liver, spleen and kidneys. Urine collection was also performed, where radioactive hydrocortisone was also located. The study confirms that hydrocortisone is released from the apex of the tooth, and distributed through the blood to the organs where it is metabolized, and excreted in the urine, showing that hydrocortisone does not accumulate in tissues or organs, as levels have decreased over time [186].

In general, few studies have investigated the relationship between the use of endodontic materials and the systemic influence that these materials can generate. There are still no studies with humans, and studies with animals carried out the implantation of the materials on their dorsum, and not in root canals, which could leave a greater amount of material in contact with the bloodstream. Despite the relevance of the results found here, they should be viewed with caution, mainly due to the different results observed and mainly regarding heavy metals.

Authors' considerations

The studies discussed in this review show the importance of endodontic medicine and the evolution of science in Endodontics about the interrelationship between apical periodontitis and systemic disorders. It is important to emphasize that the discoveries of the last few years have made us better understand this interrelationship, discarding outdated concepts from the theory of focal infection, and confirm the effectiveness of the treatment and reestablishment of health, without the need to remove the dental organ.

This understanding is only possible, because we know that the reduction in the bacterial load of the root canals associated with the use of good filling materials and the host's immune response are capable of acting on residual microorganisms from the root canals and favor the repair of periapical tissues and the health of the periodontium.

Although apical periodontitis is an infectious disease, studies of endodontic medicine reveal that its development, severity and even control are directly related to the host's immune response. Thus, the individual's organic condition greatly influences this response.In addition, it is fundamental to consider this local immune response, but exacerbated, may reflect systemically, showing mechanisms that are still unknown, but capable of triggering changes that may or not have a systemic repercussion depending on the organism of each individual or even potentiate a systemic condition.

Contrary to the well-established and frequently studied association between periodontitis and some systemic disorders, the findings on the systemic effects of endodontic materials still do not confirm this interaction. However, every endodontist should know that materials, even though they are biocompatible, are a foreign body to organism, therefore, they have the potential to trigger an immune response.

Finally, the knowledge of endodontic medicine is of paramount importance for the endodontist to provide fully assist the patient, and for interaction between dentists and doctors, providing favorable conditions of oral and systemic health for patients.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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