# Interaction between apical periodontitis and systemic disease (Review)

LANXIANG YE[1-3*], LI CAO[4*], WENCHENG SONG[1-3], CHEN YANG[1-3], QINGMING TANG[1-3] and ZHENGLIN YUAN[1-3]

[1]Department of Stomatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022; [2]School of Stomatology, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030; [3]Hubei Province Key Laboratory of Oral and Maxillofacial Development and Regeneration, Wuhan, Hubei 430022; [4]Department of Gastroenterology and Hepatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China

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**Abstract.** Apical periodontitis is an oral common inflammatory disease initiated by infection of pulp chamber and is characterized by destruction and resorption of the periapical bone. As a local infection, pathogens and their products in periapical tissues, as well as inflammatory cytokines produced in periapical lesions, enter the blood circulation, triggering systemic immune responses and leading to the pathogenesis of various types of systemic disease. Therefore, apical periodontitis might be associated with systemic disease rather than solely simple local oral disease. In addition, the existence of a hyperinflammatory state in certain patients with chronic inflammation-related disorder may affect the progression or prognosis of apical periodontitis. However, the association and potential mechanisms between apical periodontitis and systemic diseases remain unclear. An in-depth understanding of the association between apical periodontitis and systemic disease will be useful for both dentists and physicians to eliminate the possible risk factors and promote the healing of apical periodontitis and systemic disease. Thus, the aim of the present review is to introduce the potential relationship between apical periodontitis and systemic disease.

*Correspondence to:* Professor Zhenglin Yuan or Professor Qingming Tang, Department of Stomatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei 430022, P.R. China
E-mail: yuanzhenglin@hust.edu.cn
E-mail: hust_tang@hust.edu.cn

*Contributed equally

*Abbreviations:* AP, apical periodontitis; T2DM, type 2 diabetes mellitus; RCT, root canal treatment; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; CAD, coronary artery disease; CRP, C-reactive protein; ROS, reactive oxygen species; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; PAI, periapical index; RFT, root-filled teeth; RD, rheumatoid disease; RLX, raloxifene; FSH, follicle-stimulating hormone; ESRD, end-stage renal disease; TLR, toll-like receptor; LBWPB, low birth weight and preterm birth; APO, adverse pregnancy outcome

*Key words:* apical periodontitis, systemic disease, inflammation, microbiota, association

**Contents**



## 1. Introduction

Apical periodontitis (AP) is a type of chronic oral inflammatory disease characterized by destruction and absorption of alveolar bone in the periapical tissue (1,2). It is usually caused by severe caries, pulp lesions or periodontal diseases. As a type of highly prevalent oral disease, 52% of the adult population worldwide was reported to have at least one tooth with AP according to a systematic review and meta-analysis in 2021 (3). Untreated teeth with AP can lead to tooth loss, jaw osteomyelitis and systemic disease associated with mortality (4-6).

In recent years, the association between AP and systemic disease has attracted attention, leading to the concept of endodontic medicine (7). As a local infection (8), previous studies have shown that microbes and toxins in periapical lesions have access to the bloodstream from the root canal system during or following endodontic therapy of teeth (9-11). Furthermore, AP modulates the systemic immune response by modifying the levels of inflammatory cytokines, such as

C-reactive protein (CRP), tumor necrosis factor (TNF)-α, IL-6 and IL-1 (12-14). The aforementioned findings suggested that periapical inflammation is important for maintaining the health of the whole body. Furthermore, the long-term persistence of chronic inflammatory disease is implicated in systemic immune dysregulation and altered inflammatory factors in the circulation (15). Hence, chronic inflammation-associated disorder affects the status of AP, which is dependent on the antagonistic balance between the pathogenic microorganism and host immune response (16). To the best of our knowledge, however, evidence of the direct relationship between AP and systemic disease is lacking.

Over the past decades, there has been growing evidence on epidemiology (Table I) and mechanistic studies suggesting a potential link between periapical disease and systemic disease (17-19). However, the available studies (18-20) analyzing the relationship between AP and systemic disease are not comprehensive. The present review summarizes the association between AP and systemic diseases, including metabolic, autoimmune and cardiovascular disease (CVD), adverse pregnancy outcome (APO), as well as psychiatric disorder (Fig. 1). Further attention and understanding of the association between AP and systemic disease will help dentists and physicians develop innovative therapeutic proposals and promote effective healing of AP and systemic disease.

## 2. Metabolic disease

*Diabetes mellitus (DM).* Globally, DM is a chronic metabolic disease characterized by hyperglycemia owing to insulin resistance and/or a deficiency in secretion of insulin or both (21). As one of the most common types of metabolic disease, it is estimated that the prevalence of DM for all age groups worldwide will rise from 2.8% in 2000 to 4.4% in 2030 and may affect ≥693 million people in 2045 (22,23). Diabetes is accompanied by various complications (24). It is considered that oral complications in patients with diabetes, such as AP, could affect quality of life (25). As the prevalence of diabetes increases, it may lead to increasing consequences of the complications of DM, such as enhancing the inflammatory response in apical tissue and accelerating alveolar bone loss (26). There have been numerous studies on the possible association between DM and AP (27-30). Notably, there may be a bidirectional association between DM and AP (Fig 2). DM may increase the prevalence of AP, accelerate the progression of AP and undermine the efficacy of root canal treatment (RCT). However, AP can affect insulin signaling pathways or reduce insulin sensitivity, leading to increased insulin requirements and blood glucose levels.

*DM affects the prevalence, progression and prognosis of AP.* Epidemiological studies (31-35) confirm that DM is positively associated with the prevalence of AP, especially in DM patients with poor glycemic control. Segura-Egea *et al* (31) performed a retrospective cohort study in which 70 participants were divided into patients with type (T)2 DM and control group. Patients with DM had a higher prevalence of AP compared with controls. In a hospital-based population, Saleh *et al* (34) indicated that patients with DM are ≥3 times more likely to exhibit AP compared with subjects without DM. Moreover, the association between AP and DM is more pronounced in patients with poor glycemic control and long-term diabetes (33,32,36) which is consistent with other investigations (35,30,47-39). Conversely, the use of metformin and statins decreases prevalence and promote the healing of AP in diabetic patients (29,40).

In addition to affecting the prevalence of AP, DM accelerates the progression of AP. In animal studies, high sugar intake and hyperglycemic states increase susceptibility to oral infection as a result of the disruption of leukocyte function, which is also supported by a greater and unbalanced presence of pathogenic microorganisms in root canals in periapical lesions in diabetes (41,42). In a rat model of combined AP and DM, increased inflammatory infiltration, higher levels of proinflammatory cytokines (IL-17, IL-23, IL-6 and TNF-α) and larger lesion size are observed in periapical tissue (41,43). Cintra *et al* (44) hypothesized that this might be partly due to enhanced systemic inflammation of DM, which contributes to a greater destruction of the alveolar bone in the periapical lesions. For example, IL-17, as a destructive inflammatory cytokine, serves a critical role in the resorption of periapical bone (45,46). Moreover, TNF-α could also promote osteoclast differentiation and maturation by activating the NF-κB signaling pathway to trigger a decrease in osteoblast function and apoptosis, resulting in an imbalance in osteoblast-osteolysis coupling (47). Moreover, the imbalance of calcium homeostasis associated with insulin deficiency leads to bone loss (48,49). Metformin, a classical diabetic prescription drug, improves hyperglycemic conditions and enhances osteogenesis by regulating glucose metabolism, promoting cell migration and increasing angiogenesis (50,51). In addition, metformin could activate the proliferation and osteogenic differentiation of dental pulp and periodontal ligament stem cells, which serve an important role in the repair and mineralization of oral-associated bone defects (52,53). In animal studies, intramuscular injection of metformin in rats with AP is effective in decreasing the size of periapical lesions via suppression of the NF-κB signaling pathway and diminishing the hypoxia-induced apoptosis of osteoblasts (54,55). In addition, intracanal metformin decreases expression of inducible nitric oxide synthase and nitric oxide to inhibit monocyte migration in periapical tissue (56). The aforementioned results confirm the positive effect of DM on the progression of AP. By contrast, Sarmento *et al* (57) found no significant differences in bone resorption mediators between patients with DM and normoglycemic patients with AP; this may be because the sample population was too small and the DM group comprised well-controlled individuals with a mean glycated hemoglobin (HbA1c) <7%.

Previous evidence has suggested that diabetes is a key preoperative factor in evaluating the prognosis of RCT and is a common cause for tooth extraction following non-surgical RCT (58-60). The accumulation of late glycosylated products in DM prolong the treatment time of RCT and increased the rate of infection in the oral cavity (60). In a retrospective case-control study, Uğur Aydın *et al* (61) assessed changes of fractal dimension and concluded that DM has a negative effect on the healing progress of periapical lesions after RCT. In the light of clinical and radiographic healing outcomes, the success rate of RCT is significantly lower in patients with DM

Table I. Epidemiological evidence of the association between AP and systemic disease.

| Systemic disease | Study design | Main findings | Association reported | (Refs.) |
|---|---|---|---|---|
| DM | Cross-sectional | Patients with DM have a higher susceptibility to AP | Yes | (31,35,34,68) |
| | | Patients with long-term DM are predisposed to AP compared with short-term DM. | Yes | (36) |
| | | Periapical status/prevalence of AP is correlated positively with HbA1c levels in patients with T2DM | Yes | (32,33) |
| | | DM decreases the success of RCT in teeth with AP | Yes | (54,66) |
| | | T2DM does not influence the prognosis of AP | No | (70) |
| | Case-control | DM does not increase the levels of bone resorption mediators in periapical lesions | No | (57) |
| | | T2DM is independently associated with significantly greater prevalence of AP. Use of metformin or statins decreases the prevalence of AP in DM | Yes | (29) |
| | | DM has a negative effect on the prognosis of AP | Yes | (61-63) |
| | Cohort | Metformin or statins promote healing of AP | Yes | (40) |
| | | DM is a risk factor for tooth extraction after NSRCT | Yes | (58) |
| | | Patients with T2DM exhibit significantly less periapical healing compared with patients without DM | Yes | (67) |
| | Pilot | AP does not affect the glycemic control or inflammatory levels in patients with T2DM | No | (83) |
| Osteoporosis | Cross-sectional | Marginal association exists between bone mineral density and periapical radiolucency | Yes | (87) |
| | | Prevalence of AP is significantly higher in osteoporotic patients. The use of BPs decreases prevalence of AP | Yes | (92) |
| RD | Cross-sectional | Patients with RD are predisposed to AP compared with control group | Yes | (116) |
| | | RD does not increase the prevalence of RCT compared with control group | No | (119) |
| | | RD does not alter the periapical histological features or the incidence of AP | No | (121,122) |
| | | Amyloid protein is almost 5 times more frequent in periapical lesions of patients with RD than in controls | Yes | (125) |
| Autoimmune hepatitis/ nephritis | Case-control | Patients with periapical radiolucency have higher prevalence of cirrhosis-associated complications | Yes | (138) |
| | Cross-sectional | Liver transplant candidates have significantly higher prevalence of radiographic periapical lesions | Yes | (137) |
| | | ESRD is significantly associated with AP | Yes | (146,147) |
| IBD | Retrospective clinical | Patients with IBD taking immunomodulators have a higher prevalence of AP. Patients with IBD and AP have larger periapical lesions than healthy subjects | Yes | (161) |
| | Case-control | Patients with IBDs have higher prevalence of AP | Yes | (162) |
| | | IBD is associated with higher prevalence of RFT and higher percentage of RFT with AP | Yes | (165) |
| CVD | Cross-sectional | AP and endodontic burden (AP and/or RCT) are associated with CAB | Yes | (195,205) |
| | | ALEO is associated with systemic inflammatory burden and cardiovascular risk | Yes | (196) |
| | | Endodontic lesions are independently associated with CAD and ACS | Yes | (200) |

Table I. Continued.

| Systemic disease | Study design | Main findings | Association reported | (Refs.) |
|---|---|---|---|---|
| | | Patients with AP have a 2.79 times higher risk of developing CAD | Yes | (201) |
| | | There is no statistically significant positive correlation between AAP and CAD | No | (202) |
| | | Periapical lesions and root fillings are significantly associated with a first MI | Yes | (209) |
| | | CAP is moderately involved in plasma biomarker changes in hypertensive patients | Yes | (207) |
| | | AP has a potential association between endodontic infection and CVD | Yes | (216) |
| | Cohort | In patients aged ≤40 years, ALEOs are significantly associated with the age at CHD diagnosis | Yes | (199) |
| | | Young adults with AP are more likely to have early endothelial dysfunction | Yes | (215) |
| Adverse pregnancy outcome | Case-control | Pregnant people with AP are more likely to have LBWPB | Yes | (225,226) |
| | | Maternal AP is significantly associated with occurrence of PE | Yes | (227) |
| | | There is no association between maternal CAP and LBWPB | No | (231) |

HbA1c, glycated hemoglobin; T2DM, type 2 diabetes mellitus; NSRCT, non-surgical root canal treatment; ALEO, apical lesion of endodontic origin; CAD, coronary artery disease; CHD, coronary heart disease; ACS, acute coronary syndrome; AAP, asymptomatic apical periodontitis; MI, myocardial infarction; RFT, root-filled teeth; PE, preeclampsia; BP, bisphosphonate; ESRD, end-stage renal disease; LBWPB, low birth weight and preterm birth; RD, rheumatoid disease; CAP, chronic apical periodontitis.

or poor glycemic control due to impairment of the angiogenic process in DM (62,63), which is in accordance with other clinical studies (32,64-67). Similar results have been observed in patients with type 1 diabetes (68). Conversely, other studies suggest that DM does not affect the healing outcome of RCT (31,69-71). Different epidemiological methodologies may contribute to the different outcomes, including tooth type, radiographic method, assessment criteria and follow-up time. The healing of RCT in DM is a continuous process and could be affected by various factors, such as time to assess prognosis, status of general health, and control of oral reinfections. The outcomes of cross-sectional studies should be evaluated with care and more prospective studies with longer follow-up time, larger sample size and stricter control of confounding factors are required.

*AP may affect insulin requirements and blood glucose status in DM*. Inflammation is involved in the pathogenesis of DM, as inflammatory states could decrease insulin sensitivity (72). Chronic infection of AP could cause aggravated and dysregulated inflammatory response, which may result in poor glycemic control and increased insulin requirements (49,73,74). Similarly, animal experiments have showed that AP could alter insulin signaling and increase blood glucose concentrations by elevating serum inflammatory cytokines and activating the adaptive immune system (74-77). Maternal alterations in inflammation and insulin signaling pathways caused by AP may directly affect insulin resistance in adult offspring (78). In the rat model of DM, mean platelet count could be elevated in the presence of both AP and periodontitis (79). In addition, alterations in antioxidant status may be one of the potential mechanisms by which AP affects the pathogenesis of DM (80,81). AP could enhance systemic effects of DM, as shown by decreased serum albumin levels and increased uric acid concentrations in DM rats with AP (80).

The efficacy of RCT in diabetes is unknown. In a case report, a patient with DM noticed a rapid increase in insulin demand after an exacerbation of the endodontic-periodontic lesion of a tooth, while the requirement for insulin decreased suddenly within one day of the root canal preparation (82). By contrast, a prospective clinical study with a 1-year follow-up period by Arya *et al* (67) suggested that endodontic treatment does not improve the levels of HbA1c in patients with DM. Furthermore, a pilot investigation indicated that AP does not affect levels of inflammatory markers or glycemic control in patients with T2DM (83). The limited sample size and uncontrolled confounding variables may partly explain the findings of the pilot study. Moreover, the administration of metformin in some participants with combined DM and AP may be a confounding factor influence blood glucose levels, masking the contribution of AP to blood glucose. In addition, both periapical healing and HbA1c levels in diabetic patients

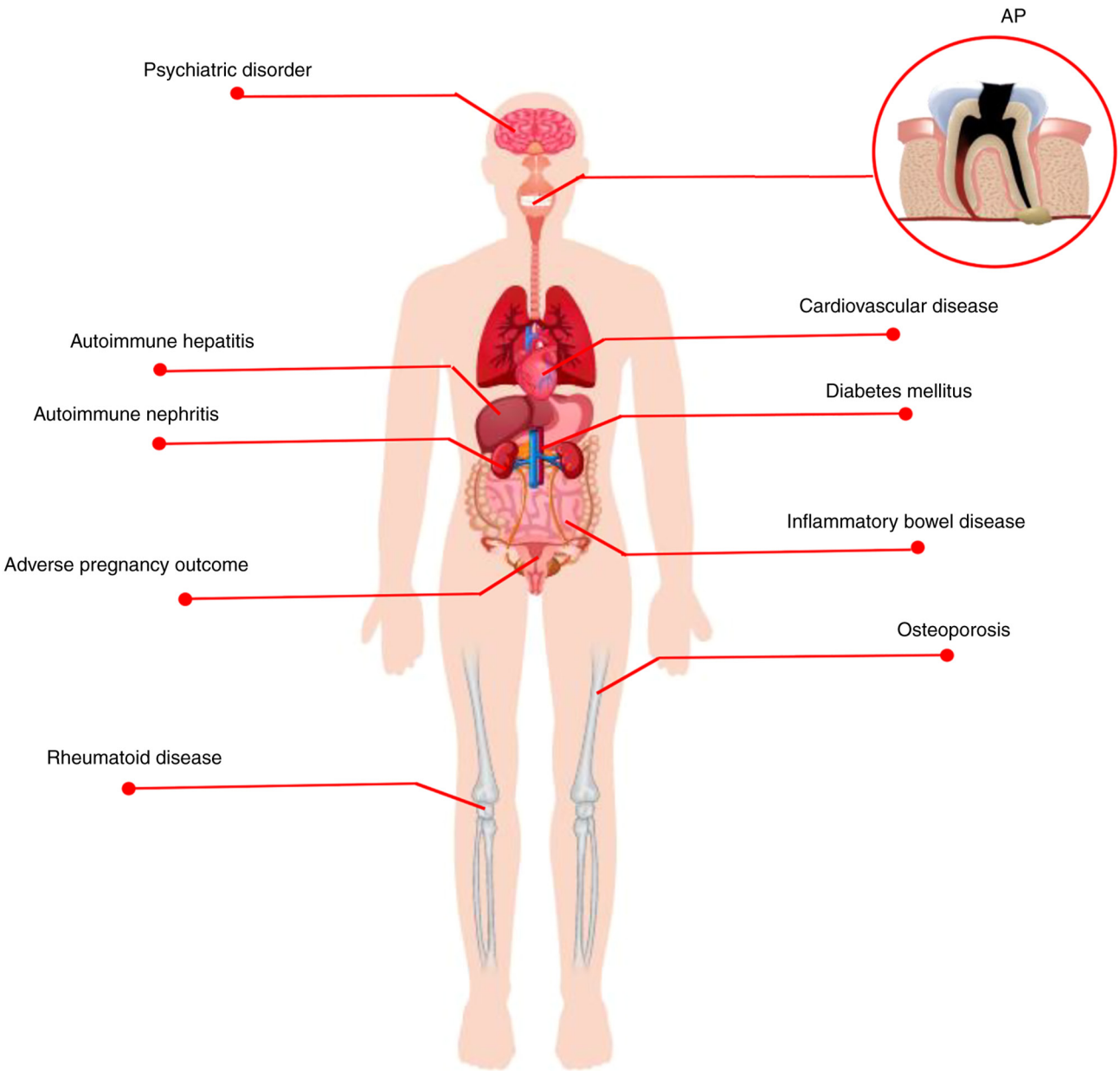


Figure 1. AP is associated with systemic disease. AP is a common oral disease associated with a number of systemic diseases, including metabolic (diabetes mellitus and osteoporosis), autoimmune (rheumatoid disease, autoimmune hepatitis/nephritis, inflammatory bowel disease) and cardiovascular diseases, adverse pregnancy outcomes, as well as psychiatric disorders. AP, apical periodontitis.

vary over time. Hence, it is critical to determine a consistent and appropriate time to assess levels of HbA1c following endodontic therapy in DM patients with AP.

In summary, there is a two-way association between DM and AP (Fig. 2). DM affects the initiation, progression and prognosis after endodontic treatment of AP. AP might affect insulin sensitivity, increase blood glucose concentrations, as well as enhance the systemic effects of DM. However, it is unclear whether endodontic treatment helps to improve insulin resistance and HbA1c levels in patients with DM and more longitudinal studies are needed.

*Osteoporosis may lead to increased AP incidence.* Osteoporosis is a common metabolic bone disorder in post-menopausal patients with estrogen deficiency and manifests as increased bone fragility due to bone loss and microarchitectural deterioration of bone tissue (84,85). Osteoporosis decreases total skeletal mass, including jawbone (86-88). Bone changes in osteoporosis are correlated with decrease of alveolar bone density and height of the alveolar ridge and loss of teeth (89-91).

Similarly, López-López *et al* (87) observed a marginal correlation between osteoporosis and radiolucent periapical lesions in post-menopausal patients. In addition, emerging evidence indicates that the prevalence of AP is higher in osteoporotic patients (92). Bisphosphonates, a type of anti-resorptive medication, inhibit the progression of AP in osteoporotic patients (92-96).

*Estrogen deficiency serves a key role in the development of AP in osteoporosis.* Systemic factors of bone remodeling in osteoporosis, such as estrogen, modify the

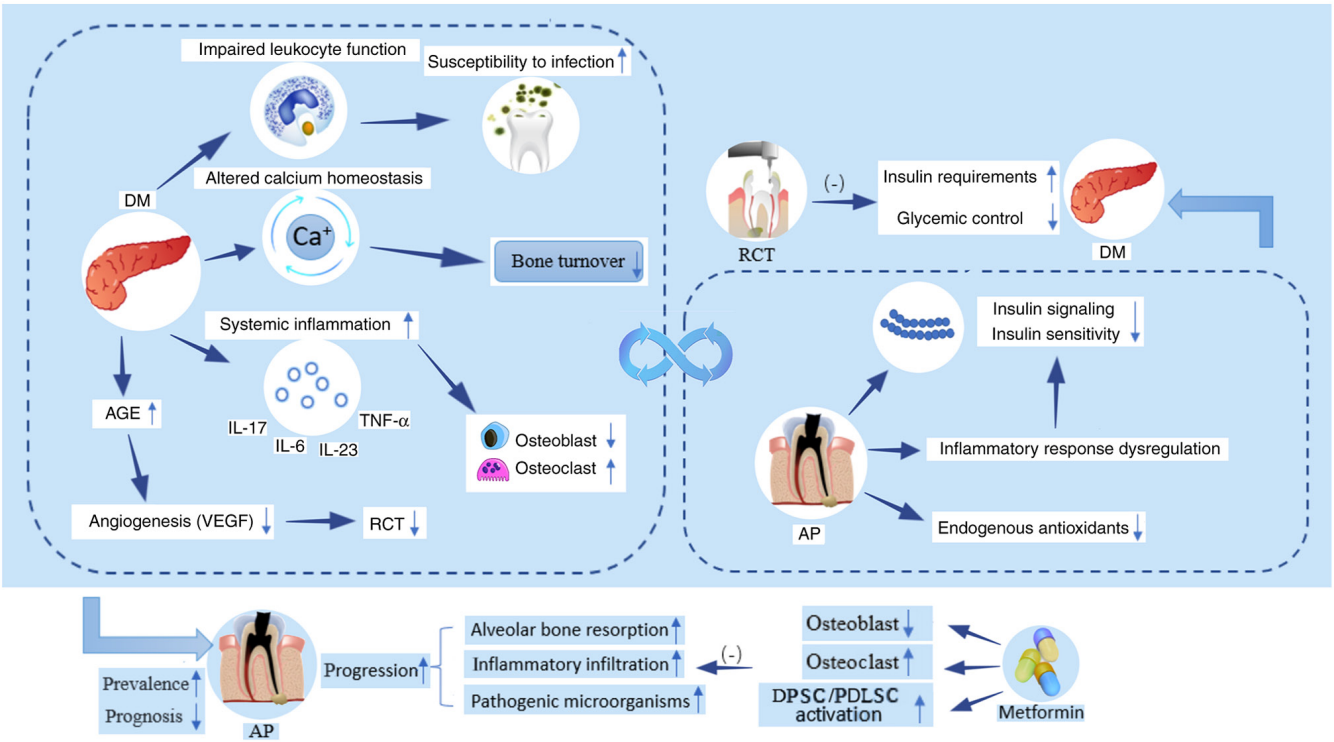


Figure 2. Bidirectional association between AP and DM. DM may affect the prevalence, progression and prognostic course of AP by elevating the oral susceptibility due to impaired leukocyte function, increasing the systemic inflammatory response (increased secretion of IL-6, IL-17, IL-23 and TNF-α), decreasing bone turnover, altering osteoblast/osteoclast homeostasis, as well as decreasing levels of VEGF and angiogenesis by accumulation of advanced glycation end-products. However, use of metformin can inhibit the negative effects of DM on AP. AP can disrupt the inflammatory response, impair insulin signaling pathways or decrease insulin sensitivity and deplete endogenous antioxidants, leading to increased insulin requirements and blood glucose levels. RCT has been shown to attenuate this adverse effect. AP, apical periodontitis; DM, diabetes mellitus; RCT, root canal treatment; AGE, advanced glycation end-product; DPSC, dental pulp stem cell; PDLSC, periodontal ligament stem cell.

balance of periapical bone metabolism. In ovariectomized animal models, estrogen deficiency serves a key role in the pathogenesis of periapical lesion by upregulating expression of members of the NLRP3/caspase-1/IL-1β axis and RANKL (95,97,98), leading to increased periapical bone resorption. The disturbed systemic inflammatory state in patients with osteoporosis is hypothesized to be the main cause of the imbalance between periapical osteoclasts and osteoblasts, which induces osteoclast apoptosis (99,100). Lucisano *et al* (101) found oral microorganisms in the saliva as well as greater periapical bone loss in ovariectomized mice compared with a control group, which indicated that decreased estrogen aggravates development of periapical lesions by altering the microbiota in saliva. Similarly, Gomes-Filho *et al* (102) simulated the effects of estrogen by administering raloxifene (RLX) in ovariectomized mice and found that RLX was able to inhibit the production of local regulators of osteoclastogenesis and angiogenesis induced by estrogen deficiency during the development of AP.

Follicle-stimulating hormone (FSH), a hormone that increases with the decrease of estrogen levels, is an independent risk factor for periapical inflammation. FSH could exacerbate bone loss in periapical lesions via directly coupling FSH receptor on the surface of osteoclasts and elevated secretion of inflammatory cytokines (103). FSH inhibitor leuprorelin has a protective effect against periapical bone loss of the experimental periapical lesions in ovariectomized rats (104).

In general, osteoporosis is considered to show a unidirectional association with AP. Osteoporosis increases incidence of AP and estrogen linking these diseases. To the best of our knowledge, however, evidence for this conclusion is limited. More robust epidemiological evidence is required to corroborate this conclusion.

### 3. Autoimmune disease (AD)

AP is a chronic inflammatory disease involving a variety of immunocompetent cells, similar to the autoimmune system, such as such as T and B cells, macrophages and immunoglobulins synthesized by plasma cells (105,106). Given the similar immunocompetent cells, it is hypothesized that there is an associate the AP with AD. Previous studies have linked types of AD to AP, such as rheumatoid and inflammatory bowel disease (IBD) and autoimmune hepatitis/nephritis (107-109).

In addition, the use of immunosuppressive agents, a conventional option for the treatment of AD, is associated with AP. It is been hypothesized that the use of immunosuppressive agents leads to weakened resistance as a consequence of decreased systemic leukocyte count, thus increasing the risk of opportunistic oral infection and susceptibility to AP (110,111). Conversely, Yamasaki *et al* (112) conducted an animal study and suggested that the long-term use of immunosuppressive agents prior to pulpal exposure significantly inhibits inflammatory expansion of AP. By contrast, Waterman *et al* (113)

and Teixeira *et al* (114) showed that use of immunosuppressive agents does not exacerbate or reduce the periapical inflammatory destruction.

The aforementioned contradictory views suggest a complex and uncertain role of the systemic immune response in AP. The pathological process of AP is determined by the balance between host immunity and virulence of the pathogen (111-113) but this dynamic balance is difficult to define. The differing findings may be related to the dose and duration of immunosuppressive agents used, as well as species or virulence of the invading bacteria.

*Rheumatoid disease (RD) is associated with a higher prevalence of AP.* Rheumatoid disease (RD) is a common autoimmune disease with a global prevalence of 0.24% in 2010 (115). A cross-sectional study conducted by Karataş *et al* (116) suggested that individuals with RD had at least two times higher risk of AP than controls. Rotstein and Katz (117) reported a similar tendency of patients with RD to develop AP based on the integrated data of hospital cases. Similarly, Oh *et al* (118) reported a clinical case of rapid destruction of periapical bone during the endodontic therapy in a patient with RD taking azathioprine. Conversely, Jalali *et al* (119) found no correlation between periapical rarefying osteitis and RD, which might be due to the restrictive diagnostic criteria of AP reducing the actual detection rate of periapical osteitis.

*Periapical alveolar bone may be a bony target of RD.* AP and RD are types of chronic inflammation involving similar inflammation markers, such as TNF-α, IL-6 and IL-17, which promote bone destruction by activating the NF-κB signaling pathway (120). In 1975, Malmström *et al* (121,122) performed a series of biopsies on periapical tissue from patients with RD and found no histological differences in periapical lesions between patients with RD and controls. However, they subsequently identified IgG, as well as other free rheumatoid factors, in periapical tissue from patients with RD (123,124). Furthermore, amyloid protein was almost five times more frequent in periapical lesions of patients with RD than in controls (125). Foxo3a, a representative protein that serves an osteolytic role in rheumatoid disease, is found in periapical tissue (126). Therefore, it is hypothesized that the periapical alveolar bone might be a bony target of RD.

Overall, most current studies (123-126) suggest a positive association between RD and AP and the osteolytic destruction of RD could also damage the periapical alveolar bone. To the best of our knowledge, however, there are few convincing studies focusing on the correlation between these diseases and the effect of AP on RD.

*Autoimmune hepatitis/nephritis.* Autoimmune hepatitis/nephritis is a chronic progressive inflammatory disease mediated by a dysfunctional immune response. Their etiology is obscure but higher susceptibility may be associated with genetics, medication and persistent infection (127-129). In the later stages of progression, severe autoimmune hepatitis/nephritis develops into end-stage liver/renal disease (ESRD), requiring liver/renal transplantation (130).

*Autoimmune hepatitis/nephritis confers higher susceptibility to AP.* Assessment of the oral health of patients with liver disease revealed that the patients with liver disease exhibit a higher frequency of oral infection (131-133), particularly in liver transplant candidates (134-136). Castellanos-Cosano *et al* (137) performed a descriptive cross-sectional study that found that the prevalence of AP in liver transplant candidates is higher than in controls, while the frequency of root-filled teeth (RFT) was lower. Furthermore, an epidemiological study by Grønkjær *et al* (138) confirmed that nearly half of patients with liver cirrhosis exhibited periapical radiolucency. These findings were confirmed by an animal study, in which increased periapical bone loss, inflammatory cell infiltration and expression of inflammatory factors in the periapical tissue were be observed in a rat model of liver fibrosis with AP (139).

Oral disease is also prominent in patients with kidney disease. Children with purpura nephritis are more likely to develop periapical infection (140,141). In patients with ESRD, oral hygiene status is worse than that of healthy individuals (142,143). Additionally, the prevalence of oral disease is associated with severity of the renal failure and worsens with length of dialysis treatment (144,145). A clinal study conducted by Buhlin *et al* (146) found that more than half of patients with ESRD have at least one tooth with periapical inflammation. In 2017, Khalighinejad *et al* (147) provided epidemiological evidence of the association between AP and ESRD and indicated that the incidence of AP is notably higher in patients with ESRD and number of AP teeth in patients with ESRD is significantly correlated with urea serum levels.

The aforementioned findings suggest that patients with autoimmune hepatitis/nephritis are at greater risk of AP compared with healthy individuals. The susceptibility of patients with autoimmune hepatitis/nephropathy to periapical inflammation may be partly attributable to liver/renal failure, loss of detoxification and accumulation of harmful metabolites, such as Urea, creatinine, uric acid, resulting in a systemic hyperinflammatory state and immunosuppression (130,148).

*AP induces autoimmune hepatitis/nephritis.* Bacterial colonies in AP (149) may be a source of infection in patients with autoimmune liver/nephropathy (140). To an extent, bacterial infections of oral origin may influence the morbidity and mortality of patients with autoimmune liver/nephropathy (150). The oral cavity is a well-known source of pathogens while the liver and kidney are key target organs for oral bacteria (151-153) Kojima *et al* (153) identified viable bacteria in hepatocytes of mice injected with *Streptococcus pyogenes*. In addition, Ogura *et al* (152) detected outer membrane antigens of *Hemophilus influenzae* (a common microorganism in AP) and specific antibodies in glomerular mesangium and serum from patients with nephritis. Moreover, there is a case report of root canal treatment of a child coincidentally inducing Henoch-Schönlein purpura nephritis (154).

The aforementioned data indicate that AP might serve a pathogenic role in autoimmune hepatitis/nephritis. The microorganisms within periapical tissue have the potential to colonize the liver/kidney either directly or by forming immune complexes, triggering a misdirected autoimmune response (152,154).

In brief, there is an interaction between AP and autoimmune hepatitis/nephritis. Extensive epidemiological evidence (137,138,146,147) suggests that patients with autoimmune hepatitis/nephritis are more likely to exhibit AP. Conversely, as an infectious source, periapical inflammation may trigger autoimmune hepatitis/nephritis. Therefore, early and thorough treatment of AP is important. In certain cases, endodontic treatment could be combined with antibiotics, especially in children who have a high propensity to develop purpura nephritis. In addition, it is essential to follow up children with Henoch Schönlein Purpura after endodontic treatment.

*Inflammatory bowel disease (IBD).* IBDs are chronic recurrent autoimmune diseases characterized by diffuse inflammation of the intestinal mucosa and include ulcerative colitis (UC) and Crohn's disease (CD), which affect any section of digestive tract (155,156). The connections between IBD and oral health (157), particularly with respect to periodontitis and dental caries, are recognized (158-160). The relationship between AP and IBDs has also gained attention (109).

*IBD is correlated with the onset and worsening of AP.* In 2017, Piras *et al* (161) showed that patients with IBD are associated with a higher incidence of AP and higher periapical index (PAI) score, especially in female patients with IBD. Similar results were also observed by Poyato-Borrego *et al* (162), who confirmed that patients with IBD have nearly six times higher risk of developing AP than healthy individuals. In addition, a case-control study suggested that the number of RFT in patients with IBD is almost four times higher than in controls (163). This may explain why patients with IBD require more dental treatment (164). However, there is no significant difference in prevalence of AP between patients with IBD and controls (165), which might be attributed to the small sample size and uncontrolled confounding factors. The increased susceptibility of patients with IBD to AP might be partially attributable to an impaired immune system, which is the primary characteristic of autoimmune disease (109,166).

In addition to increased incidence, it is hypothesized that the impaired immune system of patients with IBD has a detrimental impact on the progression and prognosis of AP (107,167). CD is a T helper (Th) 1 type of immune disease, whereas UC is defined as a Th2 type of immune disease (168). Both types of immune response are associated with the pathological process of AP. For example, activation of osteoclasts in the Th1 lymphocyte response is implicated in the progression of periapical bone destruction, while the Th2 lymphocyte response is associated with the healing of AP following RCT (169-171). Accordingly, IBD may be associated with the onset and worsening of AP.

*Microorganisms from the oral cavity link AP to IBD.* From a microscopic perspective, microorganisms originating from the oral cavity may serve a role in the link between AP and IBD (151,172). The oral cavity is the start of the gastrointestinal tract (173). Oral bacteria that enter the gut during swallowing could stimulate intestinal pathogens (necrotrophy) and create novel phenotypical bacterial virulence genes by increasing bacterial virulence (151,174). On the other hand, oral bacteria might be directly linked with digestive disease by altering intestinal flora (175). An animal study in rats by Tavares *et al* (176) demonstrated that AP can elevate the intestinal leptin levels in metabolic disorders by modulating gut microbiota. Dysbiosis of the intestinal microbiota is a common feature of intestinal diseases, including IBD (177). Recently, Gan *et al* (178) established an AP model in rat infected by *Porphyromonas gingivalis* and found that AP changed the diversity of intestinal microbiota and *P. gingivalis* was not detected in the collected stools. The aforementioned results suggest that periapical inflammation might alter the intestinal flora through multiple pathways (178). Similarly, Kojima *et al* (153) found a significantly higher detection rate of *Streptococcus mutans* in patients with IBD compared with that in controls in a clinical study. In addition, it was observed that the injection of *S. mutans* into mice is more likely to cause IBD than oral administration (153).

*Biological medications (BMs) are advocated for treatment of patients with IBD and AP.* Immunosuppressive agents are generally used to treat IBD in the clinic. However, use of immunosuppressive agents increases the risk of oral opportunistic infections and bone marrow suppression, thus increasing the susceptibility to AP or promoting further deterioration of periapical lesions (118,179). BMs are recombinant human proteins that target inflammatory factors, such as anti-TNF agents (180). Existing studies have shown that patients with IBDs and AP exhibit faster and better healing with few complications in endodontic treatment combined with anti-TNF therapy (109,181). Theoretically, anti-TNF agents block not only the direct stimulatory effect of TNF-α on osteoclasts, but also the negative effect on osteoblast activity and differentiation, which relieves destruction of periapical tissue and stimulates regeneration of supporting tissue (182). Accordingly, it is hypothesized that patients with IBD and severe treatment-resistant AP and with elevated levels of circulating TNF-α may benefit from anti-TNF treatment.

Current studies (107,161,163) suggest an association between IBD and AP. IBD shows a positive correlation with onset and progression of AP (161-163). In turn, microorganisms in AP lead to the dysbiosis and immune imbalance of the intestinal flora via multiple pathways (176,178). Conventional immunosuppressive agents may not be appropriate for patients with IBD and AP (179). Instead, targeted treatment with BMs to promote healing of systemic disease and AP is favored (180).

## 4. CVD

CVD, particularly cerebrovascular and ischemic heart disease, are primary causes of mortality and disability worldwide. An estimated 17.7 million deaths could be attributed to CVD, accounting for 31% of all deaths worldwide in 2019 (183), which is a major threat to human life (184,185). Therefore, it is key to determine the risk factors associated with CVD. The relationship between AP and CVD has been investigated for several decades and numerous reviews or meta-analyses have been published (186-189). Most studies have found a weak correlation between AP and CVD (186-191), with only a few disagree (192,193).

*Patients with CVD are at higher risk of AP.* A systematic review with meta-analysis in 2022 suggested a weak positive association between AP and CVD (194). Atherosclerosis is the main pathological basis of CVD and is highly correlated with the prevalence of AP, as shown by epidemiological studies (195,196). Additionally, Conti *et al* (197) confirmed that atherosclerosis increases the inflammatory reaction and size of periapical lesions. As one of the most common types of CVD, coronary artery disease (CAD) is associated with a higher prevalence of periapical inflammation (198-200). In comparison with non-CAD subjects, patients with CAD have a nearly threefold increase in the risk of AP (201), which is consistent with another study detected AP in 42.6% of patients with CAD and in 40.1% of non-CAD controls (202). Hypertension, a recognized primary risk factor for CVD, is also linked with a high prevalence and increased radiographic area of AP (203), and the prevalence of AP in hypertensive patients is notably decreased following treatment with angiotensin II receptor blockers (204).

*AP contributes to progression of CVD.* Gan *et al* (178) established a model of AP by inoculating *P. gingivalis* into the pulpal cavity of apolipoprotein E-deficient mice and found that AP exacerbated formation of atherosclerotic plaque in the aortic arch. Consistently, Conti *et al* (197) demonstrated that AP could promote the progression of atherosclerosis by increasing triglyceride levels and the thickness of the carotid artery intima tunic. Furthermore, endodontic therapy is hypothesized to be an effective approach to reverse the inflammatory effect of AP on atherosclerosis (205). In patients with hypertension combined with AP, AP increases levels of serum inflammatory markers such as IL-6, CRP and fibrinogen, disturbs the balance of the oxidative state and impairs cardiac function (203,206,207). Messing *et al* (208) found a positive association between AP and a single nucleotide polymorphism in potassium channel subfamily K member 3 (KCNK3), a gene that increases susceptibility to hypertension, which suggested that AP and hypertension may share a common genetic variation. AP is linked with an increased risk of first myocardial infarction (209).

*Potential mechanisms linking AP and CVD.* Numerous underlying mechanisms have been proposed for the association between AP and CVD (Fig. 3). Bacteria and/or their products may translocate from periapical tissue to various parts of the body via systemic circulation, especially areas with pre-existing cardiovascular lesions, and accelerate the progression of CVD. For example, DNA of *P. endodontalis* in monocytes (210) and elevated levels of anti-*P. endodontalis* IgG are found in peripheral circulation of patients with AP (211). In addition, Kazanci *et al* (212) reported an 8-year-old boy was admitted to hospital for acute cerebral infarct; cerebrospinal fluid cultures yielded *Streptococcus oralis* from alveolar abscess of the left maxillary first premolar. These findings are in accordance with a previous study that found bacteria and/or their products in circulation trigger low-grade systemic inflammation and contribute to the formation of plaques or thrombi (178).

Inflammatory response (197), oxidative stress (203) and endothelial dysfunction (213) are potential mechanisms underlying the interaction between AP and CVD. Inflammatory mediators serve a crucial role in the initiation and progression of both AP and CVD (196). Systemic inflammation, which is amplified by CVDs, also acts on periapical tissues by intensifying the inflammatory reaction and increasing bone resorption in periapical lesions (197). In addition, inflammatory mediators mediate endothelial dysfunction (214). Previous studies have demonstrated that patients with AP exhibit increased lipid levels and serum inflammatory mediators (TNF-α, IL-1, IL-6, IL-2 and asymmetric dimethylarginine), which implies early endothelial dysfunction (196,197,213,215). Moreover, Chauhan *et al* (216) observed impaired flow-mediated dilatation and endothelial flow reserve, as well as greater carotid intima-media thickness, in individuals with AP compared with controls in a cross-sectional study. However, successful local endodontic therapy does not ameliorate early endothelial dysfunction (215).

In terms of oxidative stress, reactive oxygen species (ROS) are by-products of cellular metabolism involved in the pathological process of both AP and atherosclerosis (217). During pulp infection, bacterial motifs bind toll-like receptors (TLRs) on the surface of phagocytes and promote synthesis and release of ROS (218). Furthermore, the dysbiosis of intestinal flora due to AP may be a source of accumulated ROS in the body (96,176). Excess ROS production directly damages the vascular endothelium and activates multiple components of the immune system, such as increasing the inflammatory cytokine expression and amplifying the neutrophil recruitment (219), which was confirmed by a study demonstrating that AP could disrupt the oxidative status and impair cardiodynamics in hypertensive rats (203). Moreover, antioxidant agent tempol exerts a prevent effect on the establishment of AP in rats with doxorubicin-induced cardiomyopathy (220).

Previous studies (194,195,197) suggest an association between AP and CVD. To the best of our knowledge, however, detailed epidemiological studies on the mechanism underlying their interaction are lacking, especially for the effect of CVD on AP. CVD is a highly complex disease with various risk factors so more well-designed animal and epidemiological studies with strict control of confounding factors are essential to clarify the causal association between these two diseases.

## 5. APO

APOs are harmful to both pregnant people and newborn infants and related with early spontaneous abortion to an extent (221,222). In particular, the alteration of hormone levels during pregnancy increases vascular permeability and accelerates the spread of inflammation (223). Maternal infection is more likely to cross the placental barrier, leading to APOs (224).

*Epidemiological evidence of the association between AP and APO.* Harjunmaa *et al* (225) found a significant association between prevalence of AP and preterm delivery and fetal growth restriction in a cross-sectional study in Malawi. Leal *et al* (226) performed a case-control study involving 63 pregnant people and found that pregnant people with AP were nearly 5 times more likely to undergo preterm labor and to deliver a low-birth weight (LBW) newborn than those without AP. In addition to the adverse effects

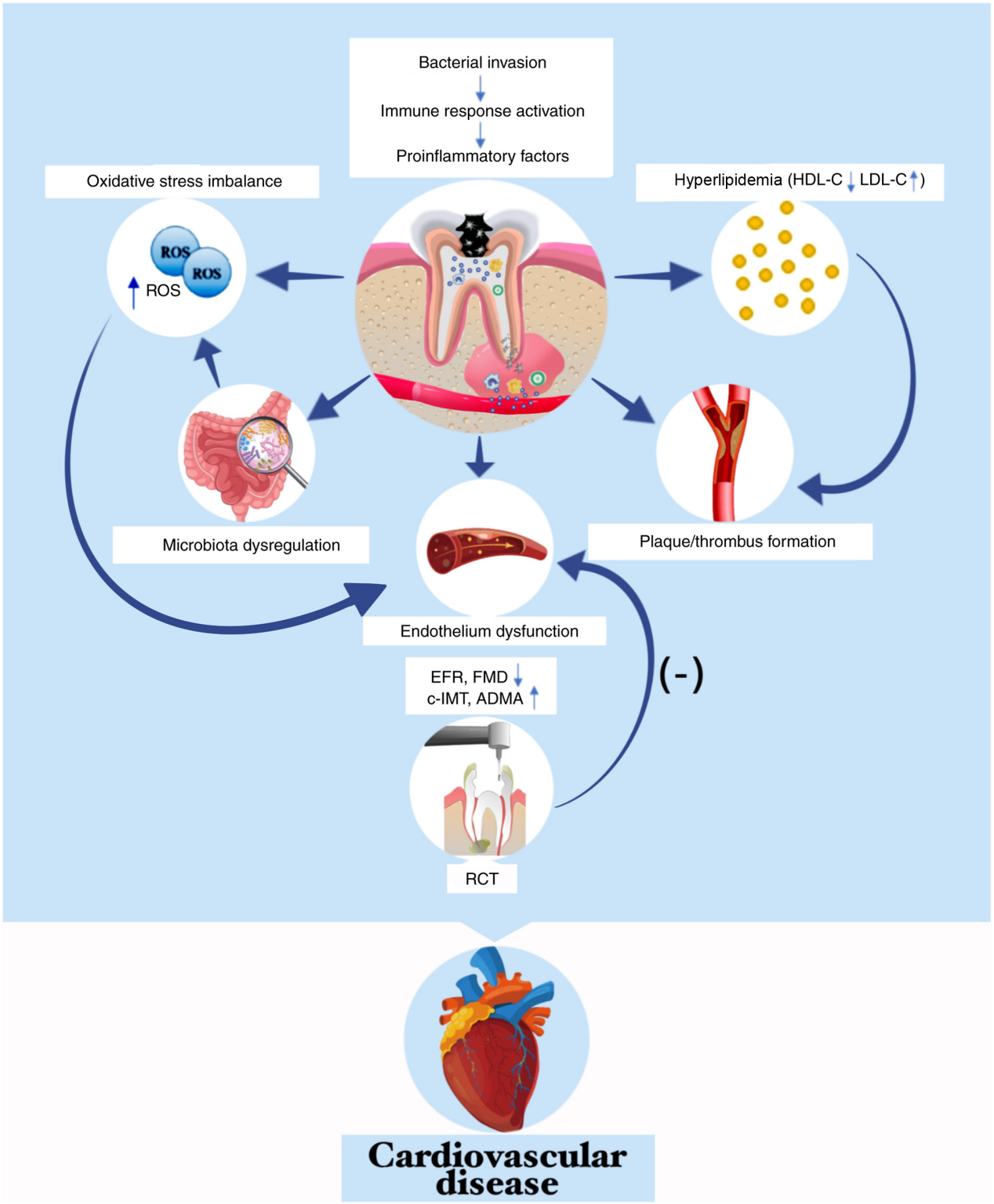


Figure 3. Apical periodontitis accelerates progression of cardiovascular disease. Bacteria and/or their products in the periapical region are transferred to systemic circulation, which can activate the systemic immune response and promote the secretion of pro-inflammatory factors, eventually causing dysbiosis of the intestinal flora, aggregating overloads of ROS and/or developing into hyperlipidemia. Elevated serum inflammatory factors and lipids contribute to plaque/thrombus formation. Excessive ROS and inflammatory mediators directly damage vascular endothelium, impairing FMD and EFR and increase c-IMT and concentration of ADMA. Conversely, root canal treatment improves early endothelial dysfunction. EFR, endothelial flow reserve; ROS, reactive oxygen species; HDL-C, high density lipid-cholesterol; LDL-C, low density lipid-cholesterol; FMD, flow-mediated dilatation; c-IMT, carotid intima-media thickness; ADMA, asymmetrical dimethylarginine.

on fetal intrauterine growth, pregnant patients with AP exhibit greater risk of developing preeclampsia compared with those without AP (227). To an extent, the likelihood of APO varies with size of the periapical lesion (226). By contrast, Bain *et al* (228,229) hypothesized that AP contributes to a higher birthweight and a longer pregnancy, which

might be related to gestational diabetes caused by insulin resistance (228-230).

Shah *et al* (231) recently conducted a cross-sectional study and found a protective association between AP and APOs, which is contrary to previous results (226,227). This result is biologically implausible, as the invasion of oral pathogens in periapical periodontitis is intrinsically harmful to the body and it can trigger a series of resistance behaviors of the body. This implausible outcome may be caused by sample selection bias, excessive loss to follow-up and uncontrolled confounding factors. Additionally, defining PAI≥3 as a diagnostic criterion for AP may underestimate the incidence of AP in the sample population (232).

*Potential underlying mechanisms of AP and APO*. To verify the relationship between AP and APO, Ao *et al* (233) created an AP model in rat infected with *P. gingivalis* and found that AP was associated with LBW and preterm birth (LBWPB). Immunohistochemistry and PCR showed *P. gingivalis* localization in placental tissue. Consistent with these results, Doyle *et al* (234) detected higher levels of *Fusobacterium nucleatum*, a representative specialized anaerobic bacteria in oral cavity, in amniotic fluid of premature infants.

The aforementioned results suggest that bacteria from periapical lesions could enter the circulation and induce temporary bacteremia, together with increased vascular permeability due to changes in hormone levels during pregnancy, which allow bacteria in the bloodstream to easily cross the placental barrier and induce maternal and fetal inflammatory reactions and immune responses. TNF-α, IL-1β and IL-6 induce premature labor, while IL-10 and vascular endothelial growth factor prevent LBW (235-238). Theoretically, maternal infection with *P. gingivalis* may inhibit expression of IL-10, thereby promoting intrauterine growth restriction; therefore, AP may induce LBWPB (239).

To the best of our knowledge, studies about the association between AP and APOs are lacking. The majority of studies show that AP is positively associated with APO. However, more studies are required to investigate the association between AP and APO and determine whether it is necessary to take preventive measures against AP in pregnant people.

## 6. Psychiatric disorder

With the rapid pace and increasing pressure of modern society, psychiatric disorders are becoming increasingly prominent, it is estimated the lifetime prevalence rates were 22.5% for any non-substance abuse mental disorder in the United States (240). Excessive stress, persistent negative emotion and severe sleep disorder affect psychiatric health to varying degrees. On one hand, psychiatric disorders affect the balance of endocrine hormone and immune response, which decreases host resistance and increases susceptibility to chronic disease (241). On the other hand, objective causes such as difficulties in maintaining oral hygiene confer susceptibility to AP. Negative mental state is involved in the underlying mechanism of various types of oral disease, such as periodontitis, oral mucosal ulcers and bruxism (241-243). For example, Maes (244) hypothesized that severe depression is accompanied by hypersecretion of adrenaline, disordered systemic immune response and activation of acute inflammatory markers, which lead to decreased host resistance and allow oral pathogens to trigger periapical lesions. Furthermore, in the dental clinic, excessive mental stress and disturbed sleep schedule are common in asymptomatic patients with AP who typically seek emergency dental treatment for acute toothache (245).

Wang *et al* (246) found that *P. gingivalis* induces a depressive phenotype. The potential mechanism may be that the free lipopolysaccharide (LPS) in the blood crosses the blood-brain barrier and downregulates expression of neurotrophic factor receptor p75 in astrocytes via the LPS/TLR4 signaling pathway (246). Furthermore, Martínez *et al* (247) detected the translocation of *Fusobacterium nucleatum* in in the frontal cortex and hypothesized that *F. nucleatum* might link oral disease to depression by inducing neuroinflammation (248). Transfer of oral bacteria across the blood-brain barrier may underlie the association between oral disease and psychiatric disorder.

*Mental stress is associated with severity of AP*. Mental stress is a state of physical or psychological tension caused by adverse mental or emotional stimuli that interferes with normal physiological functions of the body (249). Studies (250,251) have shown that the levels of catecholamines, cortisol hormones and inflammatory factors in the body are closely associated with mental stress Excessive stress stimulates secretion of catecholamines by exciting the sympathetic nervous system and activating the hypothalamic-pituitary-adrenocortical axis, promoting the release of cortisol (250,252). Cortisol regulates immunity by decreasing the number and activity of immune cells and inhibiting secretion of cytokines (253). In a survey, Haug and Marthinussen (245) found that a sudden onset of acute toothache in patients with chronic AP is typically associated with greater stress at home or work; higher levels of cortisol and inflammatory factors in saliva may be the direct cause of acute episodes of AP (254). Similarly, exogenous chronic stress exacerbates the pathological process of AP by increasing periapical bone resorption and release of inflammatory cytokines (255,256). In addition, the application of adrenergic blockers is effective in reducing the number of osteoclasts in the periapical region (257). Thus, mental stress induces imbalance between the secretion of cortisol and inflammatory factors in saliva, which is strongly correlated with the severity of AP (254).

*Sleep disorder affects progression of AP by altering hormone levels*. Sleep disorder is a common key clinical feature of psychiatric disorder (258,259). Sleep disorder is a key risk factor for oral cancer, periodontitis and adolescent maxillofacial development (260-262). Sleep disorder affects rhythmic expression of various proinflammatory cytokines and endocrine hormones, including cortisol and melatonin (263). Intraperitoneal injection or sealing of cortisol in the root canal in an AP rat model causes damage to periapical tissue and increases resorption of periapical bone (254,264). Melatonin is an important hormone with anti-inflammatory and antioxidant activity that is secreted by the pineal gland during the night (265). Melatonin suppresses oral inflammation and decreases loss of alveolar bone (266). Tavares *et al* (267) found that melatonin is a feasible adjuvant

to promote healing of periapical bone in AP by increasing the insulin sensitivity and decreasing plasma concentrations of inflammatory cytokines. In addition, Sarıtekin *et al* (268) demonstrated that systemic injection of melatonin could significantly inhibit the resorption of periapical alveolar bone and decrease plasma expression of inflammatory factors in rats with AP. Therefore, it is hypothesized that sleep disturbance may be a risk factor in exacerbating the inflammatory response of periapical tissue in AP.

Studies suggest (253,254) that the association between psychiatric disorder and AP is primarily mediated by disruption of hormone levels and the imbalance of host immunoreaction. In clinical practice, doctors should attach importance to the oral condition of patients with psychiatric disorder and provide necessary oral health education. However, due to the lack of epidemiological data and limited animal studies, the association between AP and psychiatric disorder is unclear. Therefore, more studies are needed to investigate the interaction between AP and psychiatric disorder.

## 7. Conclusion

An increasing number of studies (18-20) have investigated the association between AP and systemic disease, including animal experiments, clinical trials and epidemiological investigations. Therefore, in the diagnosis and treatment of AP, dentists should consider systemic disease and medications to assess patient condition, develop a therapeutic plan and evaluate prognosis. Physicians should be aware of the periapical status of patients with systemic disease to minimize the negative impact of AP. For example, physicians should raise awareness of oral health in patients with systemic disease associated with AP, focus on the possible adverse effects of specific drugs, such as immunosuppressants like methotrexate and cyclophosphamide, on the periapical tissue. Furthermore, physicians should collaborate with outpatient dentists for regular follow-up to better assess patient condition and oral status. As AP may be one of the etiologies or clinical manifestations of certain types of systemic disease, focusing on the interaction between AP and systemic disease will help dentists and physicians seek reasonable therapeutic options to promote the healing of AP and systemic disease as effectively as possible.

However, the majority of current studies (18,19,27) only provide the evidence of the association between AP and systemic diseases rather than a strict causal association. Associations between AP and systemic diseases are complex, which may be bidirectional or unidirectional. In addition, the association is susceptible to multiple confounding factors. It is difficult to exclude confounding factors to establish a strict causal association, as shown by a review by Segura-Egea *et al* (27). Establishment of strict causality should analyze and achieve the Hill's criteria (strength of the association, biological rationality, temporal relationship, dose-response gradient, consistency of the association). To the best of our knowledge, there are few studies (67,82) that have investigated whether RCT could decrease the epidemiological incidence or attenuate clinical symptoms of systemic disease. Therefore, clinical trials are needed to confirm AP as a potential risk factor for systemic disease. Furthermore, confounding factors and bias should be controlled as much as possible during the design process of the correlation studies, which will help to elucidate the correlation and the underlying mechanisms about the association between AP and systemic disease more convincingly.

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## Availability of data and materials

Not applicable.

## Authors' contributions

LY, LC, WS and CY wrote and revised the manuscript and constructed table and figures. QT and ZY conceived the study and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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