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Effects of periodontitis on cancer outcomes in the era of immunotherapy

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Abstract

Periodontitis results from dysbiosis of the oral microbiome and affects up to 70% of US adults aged 65 years and older. More than 50 systemic inflammatory disorders and comorbidities are associated with periodontitis, many of which overlap with immunotherapy-associated toxicities. Despite the increasing use of immunotherapy for the treatment of cancer, uncertainty remains as to whether the microbial shift associated with periodontal disease can influence response rates and tolerance to cancer immunotherapy. We herein review the pathophysiology of periodontitis and the local and systemic inflammatory conditions related to oral dysbiosis, and discuss the overlapping adverse profiles of periodontitis and immunotherapy. The effects of the presence of *Porphyromonas gingivalis,* a key pathogen in periodontitis, highlight how the oral microbiome can affect the hosts' systemic immune responses, and further research into the local and systemic influence of other microorganisms causing periodontal disease is necessary. Addressing periodontitis in an ageing population of people with cancer could have potential implications for the clinical response to (and tolerability of) immunotherapy and warrants further investigation.

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Contributors

SIP conceptualised the manuscript. All authors participated in the literature search, data collection and analysis, production of figures, and manuscript writing and revision, and accessed and verified the data.

Declaration of interests

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Introduction

The estimated national expenditures for cancer care in the USA were projected to be US$208·9 billion in 2020, compared with an estimated $137·4 billion in 2010.[1] The US Centers for Disease Control and Prevention predicts that the number of new cancer cases will increase as the population ages, resulting in a rise in the overall cost of cancer care annually. Immunotherapy has changed the treatment landscape for patients with cancer by improving overall survival and providing durable response rates, but it has toxicity profiles distinct from those of traditional cytotoxic and targeted therapies. Over 50% of patients with cancer in high-income countries are estimated to be eligible for treatment with immune checkpoint blockade (ICB) drugs.[2–4] Immunotherapy prompts the host immune system to eliminate cancer cells, but it can also inadvertently activate immune cells to recognise and target self-antigens, producing autoimmune-related toxic effects. Acute toxicities are common, and chronic immune-related adverse events reportedly affect up to 40% of patients with cancer treated with immunotherapy.[4] The toxicity profile of adverse events attributed to immunotherapy (panel) overlaps with many of the systemic inflammatory conditions possibly associated with periodontitis, such as diabetes, rheumatoid arthritis, inflammatory bowel disease, pulmonary diseases, and atherosclerotic cardiovascular disease.

According to US data,[5,6] periodontitis affects up to 70% of adults aged 65 years and older. The incidence of periodontitis is likely to be particularly high in non-Hispanic Black, Hispanic, Native American, and Alaska Native people, who tend to have poorer oral health than other US racial and ethnic groups.[7] In 2018, the aggregate cost of periodontal disease was estimated at $3·49 billion in the USA (with a total $154·06 billion in indirect losses) and €2.5 billion in Europe (with a total €158·64 billion in indirect losses).[8]

Given the economic impact of cancer care and periodontitis on the growing ageing population, we explore the potential interplay of the oral microbiome and cancer immunotherapy. More specifically, we review the causes of periodontitis and its associated systemic complications, and examine whether treating the oral microbial dysbiosis associated with periodontitis in patients with cancer could improve cancer outcomes and contribute to reducing racial cancer disparities in the era of immunotherapy.

Pathophysiology of periodontitis

Periodontitis is a chronic inflammatory disease that affects the structures supporting the teeth. Periodontitis was historically described as a simple bacterial infection, but understanding of this complex disease continues to improve and the pathogenic process behind periodontitis is now known to consist of a positive-feedback loop between the oral microbiome and the host inflammatory response directed against resident microorganisms.[9–11]

The accumulation of a bacterial biofilm (bacterial plaque) on the surface of the teeth can elicit a local immune response from the host. Inflammation confined to the gingiva, referred to as gingivitis, can be addressed through effective oral hygiene. However, the accumulation of more extensive plaque deposits at the dentogingival niche results in the enrichment

and maturation of the biofilm, sustained local inflammation, and irreversible loss of the supporting tissues (ie, connective tissue fibres, periodontal ligament, and alveolar bone), which is termed periodontitis (figure 1).[12] Initially, the biofilm consists of mostly Gram-positive bacteria (eg, *Streptococcus* spp, *Staphylococcus* spp, and *Rothia* spp), followed by Gram-positive bacilli (eg, *Actinomyces* spp and *Corynebacterium* spp) and a small number of Gram-negative cocci.[13] As the bacteria divide, an intricate three-dimensional network or extracellular matrix develops and provides a protective environment for the bacteria. This extracellular matrix allows Gram-negative anaerobic bacteria to thrive deep within the oral biofilm, protected from the oxygen-rich environment of the oral cavity. The systemic effects of periodontitis might be attributable to systemic increases in proinflammatory cytokines such as IL-6,[14] complement factors, and signalling pathways elicited by multiple bacteria. In this Review, we focus on one of the most studied and common oral pathogens associated with periodontitis, *Porphyromonas gingivalis*,[10,15,16] to highlight how the oral microbiome can affect systemic host immune responses and elicit an autoimmunity profile that overlaps with immune-related adverse events associated with immunotherapy (panel). *P gingivalis* is a pathogenic, non-motile, Gram-negative anaerobic species of bacteria typically not abundant in the healthy oral cavity. *P gingivalis* expresses several virulence factors that aid in proliferation, overgrowth, and survival within the oral cavity, and that support adhesion with other bacterial species, polymicrobial colonisation, and maturation of the biofilm, having a key role in aggregating necessary nutrients (eg, nitrogen, carbon, and iron) to support bacterial growth and function (figure 2).

P gingivalis virulence factors and bacterial clearance

P gingivalis expresses several virulence factors, such as gingipains, lipopolysaccharides, outer membrane vesicles, and fimbriae. These molecules have a key role in bacterial evasion to host immune recognition and clearance, by triggering cleavage of the antibodies that mediate opsonisation and by degrading or downregulating some proinflammatory cytokines and chemokines, which can reduce the efficacy of immune cells recruited to clear the bacteria (figure 2). *P gingivalis* can thus uncouple bacterial clearance from inflammation and consequently promote dysbiotic conditions through several mechanisms, such as upregulation of selectins and of the complement and PD-1–PD-L1 pathways.

Effect of gingipains on the complement pathway

The complement pathway is a signalling cascade that helps the immune system rapidly clear pathogens by promoting inflammation and the recruitment of phagocytic cells to sites of infection. *P gingivalis* can subvert the complement pathway to inhibit bacterial killing but preserve inflammation[16] by expressing gingipains, which proactively generate C5a[17] and activate the C5a receptors expressed by neutrophils, eosinophils, basophils, monocytes, and mast cells.[18,19] Through crosstalk between TLR2 and C5a receptors, *P gingivalis* can degrade MYD88 (which blocks phagocytosis by neutrophils) and subsequently activate the PI3K pathway (which promotes inflammation). Other studies have shown that patients with periodontitis have higher serum concentrations of complement C3 than do healthy controls.[20] The C3A receptor (C3AR)-mediated and C5AR1-mediated pathways have been shown to suppress effector T-cell function,[21,22] which suggests that untreated periodontitis

might hamper response to immunotherapy.[23–25] Magrini and colleagues[23] investigated the influence of complement C3 or C3AR expression on the efficacy of anti-PD-1 therapy. They reported that treating an MN/MCA1 sarcoma preclinical model with an anti-PD-1 monoclonal antibody resulted in little antitumour activity, whereas treating homozygous *C3*-deficient mice with anti-PD-1 therapy resulted in significant tumour growth inhibition; in addition, anti-PD-1 treatment prevented lung metastasis in the *C3*-deficient metastatic MN/MCA1 sarcoma model.[23] Similarly, Zha and colleagues[24] reported that the presence of C5a negatively affected the effectiveness of PD-1 blockade in a preclinical MC38 colon adenocarcinoma model. This result was corroborated in another preclinical model of non-small-cell lung carcinoma, in which protection against cancer growth and metastasis was achieved with dual blockade of PD-1 and C5a and C5a receptor.[25] These findings suggest that overexpression of *C3* or *C5* can negatively affect the efficacy of ICB therapy.

FimA and the PD-1–PD-L1 immune checkpoint pathway

The antigen-induced activation and proliferation of T cells are regulated by the temporally regulated expression of both co-stimulatory and co-inhibitory receptors and their cognate ligands. Coordinated signalling through these receptors modulates the initiation, amplification, and subsequent resolution of adaptive immune responses. In the absence of co-inhibitory signalling, persistent T-cell activation can lead to autoimmunity and excessive tissue damage in the site of infection. In the context of infection, in which immune responses are directed against antigens selectively expressed by a bacterial or viral pathogen, these immune checkpoints can be obstacles to the generation and maintenance of effective immune responses that can clear the infection. The PD-1–PD-L1 cascade is an immune checkpoint pathway that has been shown to be upregulated in $CD8^+$ and $CD4^+$ T cells in oropharyngeal cancers associated with human papillomavirus, as a viral mechanism to evade immune clearance.[26,27] Several studies have also shown increased expression of PD-1 and PD-L1 in periodontal tissue, the gingival sulcus, and peripheral blood of patients with periodontitis, which is attributed to the fimA protein.[28–31] This virulence factor expressed on the surface of *P gingivalis* stimulates T cells and $CD11b^+$ cells to generate IL-10, inducing PD-1 expression on $CD4^+$ T cells,[32] whereas the outer membrane vesicle of *P gingivalis* induces PD-L1 expression in $CD11b^+$ and other cells.[32,33] The subsequent activation of the PD-1–PD-L1 pathway within the periodontal microenvironment results in T-cell anergy and facilitates bacterial persistence. Other immune checkpoint molecules have also been reported to be overexpressed in periodontitis, such as CTLA4[34,35] and TIM3 (HAVcr-2).[36] Periodontitis-induced systemic upregulation of several immune checkpoint pathways might also have a role in the development and progression of periodontitis-related systemic disorders.[37]

The role of selectins in bacteraemia and systemic inflammation

Selectins are cell adhesion molecules expressed by leukocytes (in which case they are named L-selectins), platelets (named P-selectins), and endothelial cells (named E-selectins) that regulate inflammatory and immune responses. Several studies[38–41] have shown high E-selectin and P-selectin expression in the gingival endothelial cells of patients with periodontitis. In the presence of periodontitis, the integrity of the periodontal epithelial pocket deteriorates progressively, facilitating the entry of bacteria and bacterial virulence

factors into the bloodstream and resulting in bacteraemia and systemic inflammation. The systemic inflammation caused by periodontitis is attributed to the release of proinflammatory cytokines, leukocytosis, and changes in the endothelial cells and platelets in the circulatory system. Selectins contribute to systemic inflammation by mediating leukocyte recruitment and platelet activation and by facilitating endothelial barrier permeability. Thus, selectins and their ligands are important factors connecting periodontal inflammation and the development of systemic disorders associated with periodontitis.[38]

Periodontitis and the gut microbiome

P gingivalis secretes a collagenase and proteases that promote collagen degradation, a hallmark of periodontal disease. The ulcerated epithelium of the periodontal pocket can facilitate the translocation of bacteria to the bloodstream and distant sites, such as the gastrointestinal tract. Due to the persistent translocation of resident bacteria from periodontal tissues into the circulation, the bacterial phyla in stool can be affected by the oral microbiome.[42] After establishing residence in the gut microbiome, *P gingivalis* infection can cause a microbial shift in the gut, as it also does in the oral cavity. An exploratory study of the gut microbiota in individuals with periodontal disease[42] showed that patients with periodontal disease had reduced diversity in the gut microbiota, and detected oral taxa in a high number of all stool samples. *Prevotella* spp, *Comamonadaceae* spp, and Lactobacillales were detected in the gut in high abundance in patients with gingivitis, and the presence of *Ruminococcaceae* spp and *Prevotella* spp allowed discrimination of individuals with periodontal disease.[42] The ability of oral pathogens to facilitate the uncontrolled growth of the commensal microbial community[43] has important implications in the setting of cancer immunotherapy. Dai and colleagues[44] reviewed several studies[45–51] on gut bacterial species enriched in clinical responders and non-responders to anti-PD-1, anti-PD-L1, and anti-CTLA4 antibodies; 57 bacteria strains belonging to six different phyla were identified as potential modifiers of ICB response. Of these 57, nine (*Collinsella stercoris*, Bacteroidales, *Bacteroides mediterraneensis*, *Prevotella histicola*, *Enterococcus casseliflavus*, *Roseburia intestinalis*, *Ruminococcus bromii*, *Staphylococcus haemolyticus,* and *Rothia kristinae*) were predominant in non-responders, and 47 were prevalent in the intestinal microbiota of responders to ICB. Matson and colleagues[48] found that *Ruminococcus obeum* was enriched in non-responders to anti-PD-1–PD-L1 therapy. Both *Ruminococcus* spp and *Prevotella* spp are common in patients with periodontitis and in non-responders to ICB, suggesting that periodontitis might influence responses to cancer immunotherapy (figure 3).

Several preclinical studies evaluated the effect of periodontitis, specifically *P gingivalis*, on mice gut microbiota through oral administration of this pathogen, and observed an increase in the proliferation of Bacteroidales and *Prevotella* spp,[52,53] which are associated with a poor response to ICB.[44] Accordingly, the populations of bacteria belonging to the Actinobacteria and Proteobacteria phyla,[43] both of which are found in clinical responders to ICB,[44] were reduced in mice with periodontitis.The ability of *P gingivalis* to shift the intestinal microbiome to a colonisation that is associated with poor responses to ICB therapies provides a rationale for further investigation of the potential relationship between the periodontitis-associated microbiome and response to ICB.

Autoimmune diseases, periodontitis, and toxic effects associated with immunotherapy

Several lines of evidence suggest that systemic immune reprogramming and activation occur in patients with periodontitis. First, early clinical signs of relapse in periodontitis (ie, bleeding on probing and probing pocket depth) are associated with increased expression of PD-1 on peripheral blood mononuclear cells from patients with periodontitis, compared with individuals without periodontitis.[30] Second, periodontitis is associated with increased numbers of neutrophils in circulation.[54] Third, high amounts of systemic proinflammatory mediators (such as IL-1, IL-6, CRP, and fibrinogen) can be detected in patients with periodontitis.[14] Lastly, periodontitis can cause microbial shifts in the oral and gut microbiome that can lead to a systemic proinflammatory state.

Over 50 systemic inflammatory diseases and comorbidities have been hypothesised to be linked to periodontitis, and many of them overlap with immune-related adverse events associated with immunotherapy (panel; figure 4).[55] The incidence of grade 3 or grade 4 immune-related adverse events is approximately 10–15% for patients with cancer receiving anti-PD-1 blocking agents such as nivolumab and pembrolizumab; 20–30% for patients receiving ipilimumab (anti-CTLA4); and 55% for patients receiving anti-CTLA4 and anti-PD-1 combination therapy.[56] Because periodontitis can alter host immune homoeostasis, periodontitis might also lower the threshold for the development of immune-related adverse events in patients with cancer treated with immunotherapy. This concept has not yet been explored in depth, but we highlight several overlapping autoimmune disorders associated with periodontitis and immune-related adverse events associated with ICB, which supports a potential negative interplay (figure 4).

Myocarditis

P gingivalis has been reported to elicit autoimmune myocarditis through increased $CD11b^+$ cells, cytokines, and MMP-9 expression in preclinical models.[57] Peron and colleagues[58] showed the capacity of translocated *P gingivalis* to induce myocarditis in healthy rats, as evidenced by increased oxidative stress and inflammatory macrophage infiltrate in the myocardium, accompanied by left ventricular systolic and diastolic dysfunction and myocardial necrosis, apoptosis, and fibrosis.

Aberrant activation of autoreactive T cells is speculated to be the cause of immune-related adverse events from anti-PD-1 or anti-CTLA4 therapy.[59,60] Pharmacovigilance studies showed that myocarditis occurred in 0·27% of patients receiving combination immunotherapy.[61] Johnson and colleagues[61] detected $CD68^+$ infiltrating macrophages within the myocardium and skeletal muscle of two patients with fulminant myocarditis treated with ICB. Given this evidence, periodontitis and the possible presence of *P gingivalis* in the myocardium might conceivably increase the risk of myocarditis in a patient with a proinflammatory baseline state, and that risk can be further compounded when ICB treatment is initiated.

Colitis

The incidence of colitis in patients with cancer treated with ICB is estimated at 3% with anti-PD-1 monotherapy and 24% with combination therapy.[62] Periodontitis and inflammatory bowel diseases display a bidirectional relationship, which is supported by the observation of spontaneous development of periodontitis in SAMP1/YitFc mice (a murine model of Crohn's disease)[63] and of intestinal inflammation caused by the periodontal pathogens that induce gut dysbiosis in mice and humans.[64–66] In mice, the induction of periodontitis by oral gavage with *P gingivalis* alone or with other periodontal pathogens (eg, *Fusobacterium nucleatum* and *Prevotella intermedia*) altered the gut microbiota[52,67] and resulted in increased expression of inflammatory cytokines in the colon.[52] In addition, ectopic colonisation of the gut by *Klebsiella* spp and *Enterobacter* spp (oral pathobionts) promoted colitis through induction of non-canonical, inflammasome-dependent IL-1β secretion by $Ly6c^{10}$, $MHCII^{hi}$, and $CD64^{hi}$ inflammatory macrophages in preclinical models.[65] Furthermore, individuals with periodontitis have a decreased abundance of Bacteroidetes in stool samples,[42] and the observation that patients with cancer treated with ipilimumab who developed colitis had a decreased abundance of Bacteroidaceae in the intestinal microbiome further supports a potential synergistic interaction between periodontitis and ICB-induced colitis.[68]

Diabetes

Endocrine toxic effects induced by ICB can occur in up to 40% of patients with cancer.[69] ICB-associated diabetes manifests as a severe and persistent resistance to insulin,[70] and can occur between 1 week and 52 weeks after the first dose of ICB.[71] Although ICB-associated diabetes is presumptively caused by immune destruction of pancreatic β cells,[72] exacerbation of underlying type 2 diabetes can also occur in patients treated with ICB.[73]

Translocation of *P gingivalis* to the nuclear and perinuclear regions of β cells, but not α cells, was reported by Ilievski and colleagues.[74] The translocation of this pathogen culminates in complex alterations in the morphology of pancreatic islets[75] and induces a prediabetic profile characterised by β-cell dysfunction and apoptosis and increased production of insulin.[74–76] Diabetes induces a hyperinflammatory response to the periodontal microbiota, impairs the resolution of inflammation and repair, and promotes a more destructive profile of periodontal diseases.[77]

The negative overlapping effect of PD-1–PD-L1 blockade and periodontitis in β cells in pancreatic islets could increase the incidence and severity of ICB-associated diabetes and worsen periodontitis, resulting in a positive-feedback loop. The multifactorial relationship between periodontitis, ICB, and diabetes needs to be further assessed in future research.

Rheumatoid arthritis

A link between periodontitis and rheumatoid arthritis has also been reported.[78] A meta-analysis[79] found a higher prevalence of rheumatoid arthritis in patients with periodontitis compared with controls and non-surgical periodontal treatment in individuals with rheumatoid arthritis reduced the levels of serum markers of disease severity in rheumatoid arthritis.[80] The development of autoantibodies against citrullinated proteins

is a known pathological factor for the development of rheumatoid arthritis. Protein citrullination is carried out by peptidylarginine deiminases, and *P gingivalis* is the only known microorganism to express a peptidylarginine deiminase.[81] *P gingivalis* has also been isolated from the synovial fluid of patients with rheumatoid arthritis.[82] *P gingivalis*' peptidylarginine deiminase has been theorised to break immunotolerance to citrullinated proteins, leading to the development of rheumatoid arthritis.[81] A preclinical study showed that a peptidylarginine deiminase-deficient strain of *P gingivalis* was associated with significantly less periodontal inflammation than was wild-type *P gingivalis*, and that previous inoculation with the peptidylarginine deiminase-deficient strain reduced the extent of induced arthritis when compared with wild-type *P gingivalis*.[83] ICB-induced arthritis occurs in up to 7% of patients with cancer,[84] but the incidence of ICB-induced arthritis in patients with periodontitis treated with immunotherapy is unknown and needs further exploration.

Sjögren's syndrome

Sjögren's syndrome is an autoimmune disorder that affects the lacrimal and salivary glands and can involve other organ systems. In a study of 135 190 patients,[85] 27 041 patients with periodontal disease were matched by gender, age, urbanisation, and income in a ratio of 1:4 of cases and controls. The patients were followed up for approximately 7 years, and 3292 of 135 190 (2·4%) patients developed Sj*ö*gren's syndrome. Patients with periodontal disease had a significantly higher risk of developing Sjögren's syndrome (adjusted hazard ratio 1·47 [95% CI 1·36–1·59]) than did patients without periodontal disease.[85] In a meta-analysis of five studies including 6926 participants, Yang and colleagues[86] also found a positive correlation between periodontitis and Sjögren's syndrome (odds ratio 2·12 [95% CI 1·43–3·17]).

Sjögren's syndrome as an immune-related adverse event has been reported in patients with cancer treated with ICB. In a study of an international cancer patient registry from 18 countries, 26 patients treated with ICB were identified as having symptoms or histopathological findings consistent with Sjögren's syndrome.[87] In this population, ICB-associated Sjögren's syndrome had a different clinicodemographic profile from idiopathic Sjögren's syndrome, with a higher occurrence in men and higher mean age when associated with ICB than in idiopathic cases. Other case reports of Sjögren's syndrome as an immune-related adverse event after ICB therapy[88,89] highlight a possible association between Sjögren's syndrome and exposure to ICB.

Treatment of periodontitis and risk of immune-related toxic effects from immunotherapy

The management of periodontal inflammation and diseases varies with the disease stage. Routine tooth brushing can reduce plaque and the development of gingivitis, which can prevent periodontitis. However, once periodontitis develops, professional care is required. A Clinical Practice Guideline[90] published in 2020 endorses the mechanical removal (scaling and root planing) of supragingival and subgingival microbial deposits as the most recommended intervention for the treatment of periodontitis. A systematic review[91]

also showed that scaling and root planing reduces the cardiometabolic risk and systemic inflammation in patients with periodontitis,[91] highlighting how the treatment of periodontitis can be a non-pharmacological approach to improve general health and quality of life.

As the understanding of the pathophysiology of periodontitis evolves, more targeted and effective therapeutic approaches can be developed. An and colleagues[92] tested a monoclonal antibody against the *P gingivalis* gingipain haemoglobin-binding domain for the treatment of experimental periodontitis in mice and concluded that the intervention significantly reduced bone loss compared with other treatments. In addition to targeting the microorganisms associated with periodontitis, therapies to restrict local inflammation have also been studied. As an example, targeted inhibition of specialised proresolving mediators not only blocked the progression of the periodontal disease, but also promoted the resolution of the disease and tissue regeneration.[93] The efficacy of these approaches in restoring systemic balance to the multiple organs affected by periodontitis has yet to be assessed.

Knowledge gaps and future perspectives

Several clinical questions regarding the potential effects of periodontitis on immune-related toxic effects and response to cancer immunotherapy remain and require further investigation. Standard mechanical treatment of periodontitis can restore the periodontium to a healthy condition. However, whether the local treatment of periodontal disease can also re-equilibrate host immune health (both locally and systemically) by shifting the oral and gut microbiome to baseline health conditions is yet to be established. Another as of yet unanswered question is whether targeting serum inflammatory markers, specific periodontal pathogens (eg, *P gingivalis*), and associated key virulence factors improves response to ICB in patients with cancer. On the basis of the current knowledge and literature, we provide a rationale for why patients with cancer should be evaluated and treated for periodontal disease before the initiation of immunotherapy. To maintain dental health, these patients should also be included in short-term follow-up periods for supportive periodontal therapy. Because non-Hispanic Black, Hispanic, Native American, and Alaska Native people generally have the poorest oral health compared with other US racial and ethnic groups, we hypothesise that managing periodontitis could help to reduce cancer disparities by improving response rates and reducing ICB toxicity profiles in underrepresented minorities and individuals with a lower socioeconomic status. Due to the high costs of these novel drugs, immune checkpoint inhibitors are more often used in high-income countries and, accordingly, most of the literature on immunotherapy comes from these regions. An unmet need to increase access to these drugs in low-income and middle-income countries persists, and might allow a better understanding of response rates across a broader patient population who might also have little access to periodontal care.

With only an estimated 12·5% of treated patients responding to ICB therapy,[2] the clinical response to immune checkpoint inhibition is still low. Therefore, a considerable effort in the immuno-oncology field focuses on improving clinical response rates and mitigating the toxic effects associated with ICB. Although the interplay between periodontitis and systemic inflammatory diseases is well established, we highlight clinical and preclinical data showing that periodontitis might influence response rates and tolerability to immunotherapy,

suggesting new opportunities for collaboration between multidisciplinary clinical teams and translational and basic scientists. More research needs to be conducted on this complex topic, and the results of such studies might bring improvements to the treatment of a growing number of individuals living with both cancer and periodontitis in a globally ageing population.

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Panel: Immunotherapy-related adverse events

Circulatory system

Haemolytic anaemia; acquired thrombotic thrombocytopenic purpura; haemolytic uraemic syndrome; aplastic anaemia; lymphopenia; immune thrombocytopenia; acquired haemophilia A; myocarditis; pericarditis; arrhythmias; impaired ventricular function with heart failure; vasculitis; venous thromboembolism

Endocrine system

Primary hypothyroidism; hypoparathyroidism; thyrotoxicosis; primary adrenal insufficiency; hypophysitis; type 1 diabetes

Gastrointestinal system

Colitis; hepatitis; pancreatitis; gastritis; duodenitis

Integumentary system

Rash or inflammatory dermatitis; bullous dermatoses; severe cutaneous adverse reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, and drug reactions with eosinophilia and systemic symptoms or drug-induced hypersensitivity syndrome)

Musculoskeletal system

Rheumatoid arthritis; myositis; polymyalgia-like syndrome

Nervous system

Myasthenia gravis; Guillain-Barré syndrome; peripheral neuropathy; autonomic neuropathy; aseptic meningitis; encephalitis; demyelinating diseases (eg, multiple sclerosis, transverse myelitis, acute-disseminated encephalomyelitis, optic neuritis, and neuromyelitis optica)

Ocular system

Uveitis; iritis; episcleritis

Respiratory system

Pneumonitis

Urinary system

Nephritis or acute kidney injury

Search strategy and selection criteria

References for this Review were identified through a search of PubMed for articles published between January 1, 1996, and January 29, 2023, with the keywords “periodontitis” AND “immune-related adverse event”, and no language restrictions. No results were found with these search words. Subsequently, other searches using the keywords “periodontitis” AND “cancer immunotherapy response” OR “oral microbiota” AND “cancer immunotherapy response” were done. Of 95 articles resulting from this search, five relevant references were reviewed and included in the paper on the basis of relevance to periodontal disease and cancer immunotherapy. We did not identify any publications that comprehensively reviewed this subject. Due to the nature of this topic, the Review is based on our multidisciplinary approach and clinical expertise pertaining to oral polymicrobial infections and cancer immunotherapy.

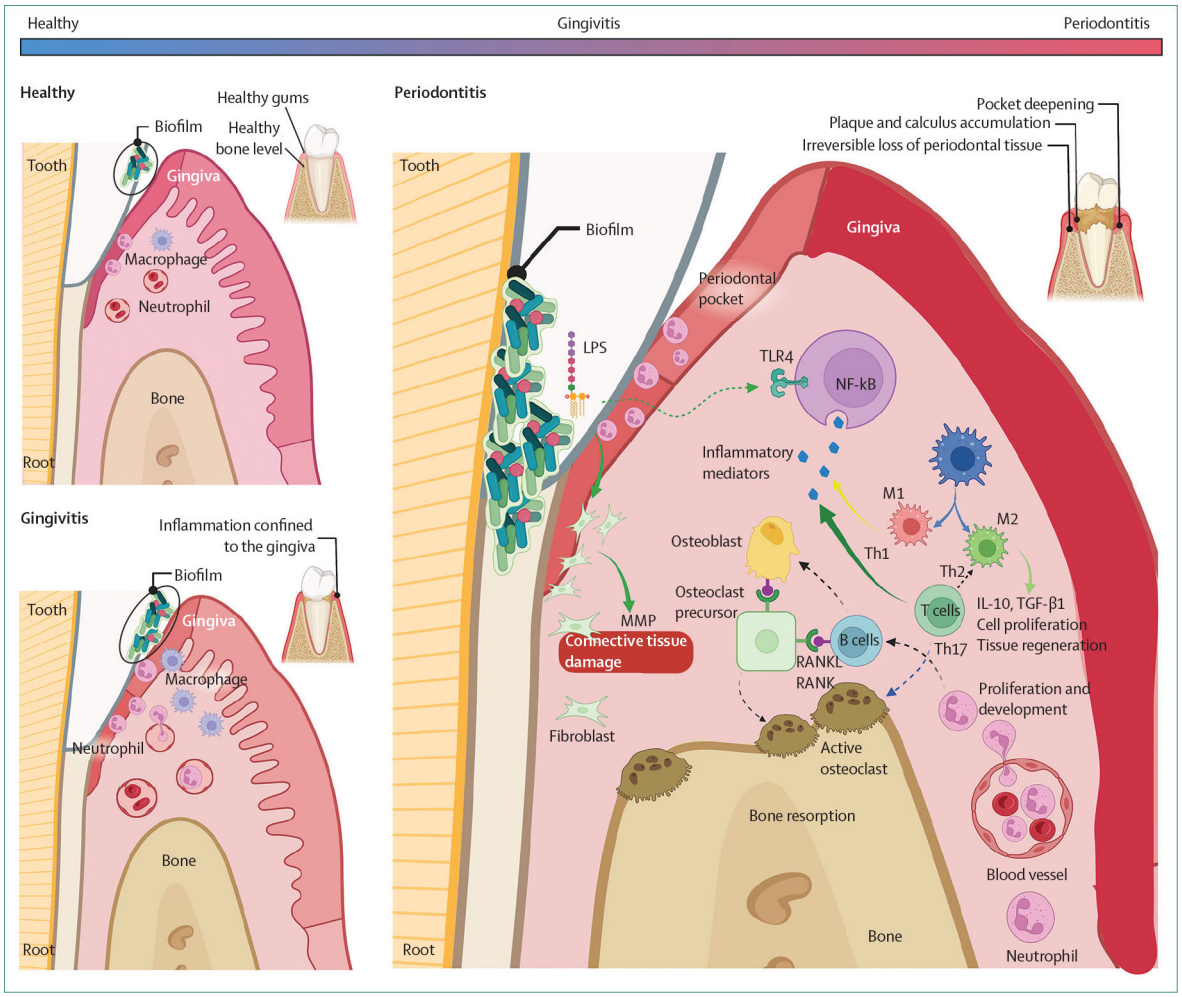

Figure 1: The clinicopathological progression of plaque-induced periodontal diseases

Illustration of the clinical, cellular, and molecular changes occurring during the progression from a healthy to a disrupted periodontium. Adapted from Muñoz-Carrillo and colleagues.[12] Figure created with BioRender.com. LPS=lipopolysaccharides. MMP=matrix metalloproteinase. Th=T helper cell.

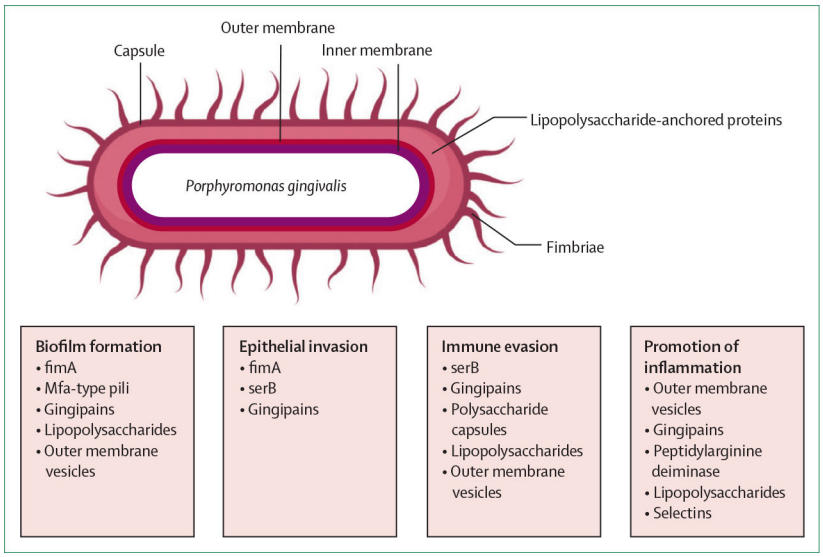

Figure 2: Virulence factors expressed by *Porphyromonas gingivalis*

P gingivalis releases virulence factors that promote biofilm formation and maturation, immune evasion, epithelial invasion, and inflammation, inducing dysbiosis in the setting of chronic inflammation.

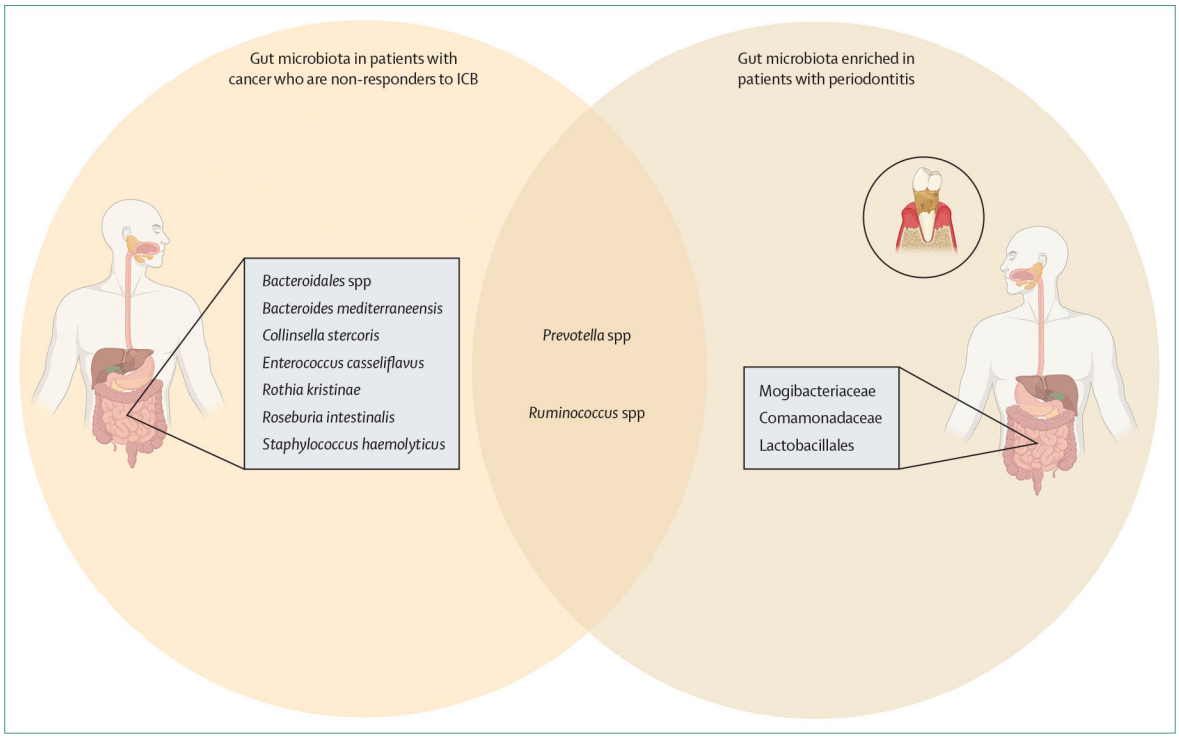

Figure 3: Similarities and differences in the gut microbiota of patients with periodontitis and patients with cancer who do not respond to ICB

Ruminococcaceae spp and *Prevotella* spp are both common to these patient populations, suggesting that periodontitis might have the potential to affect the response to immunotherapy. Figure created with BioRender.com. ICB=immune checkpoint blockade.

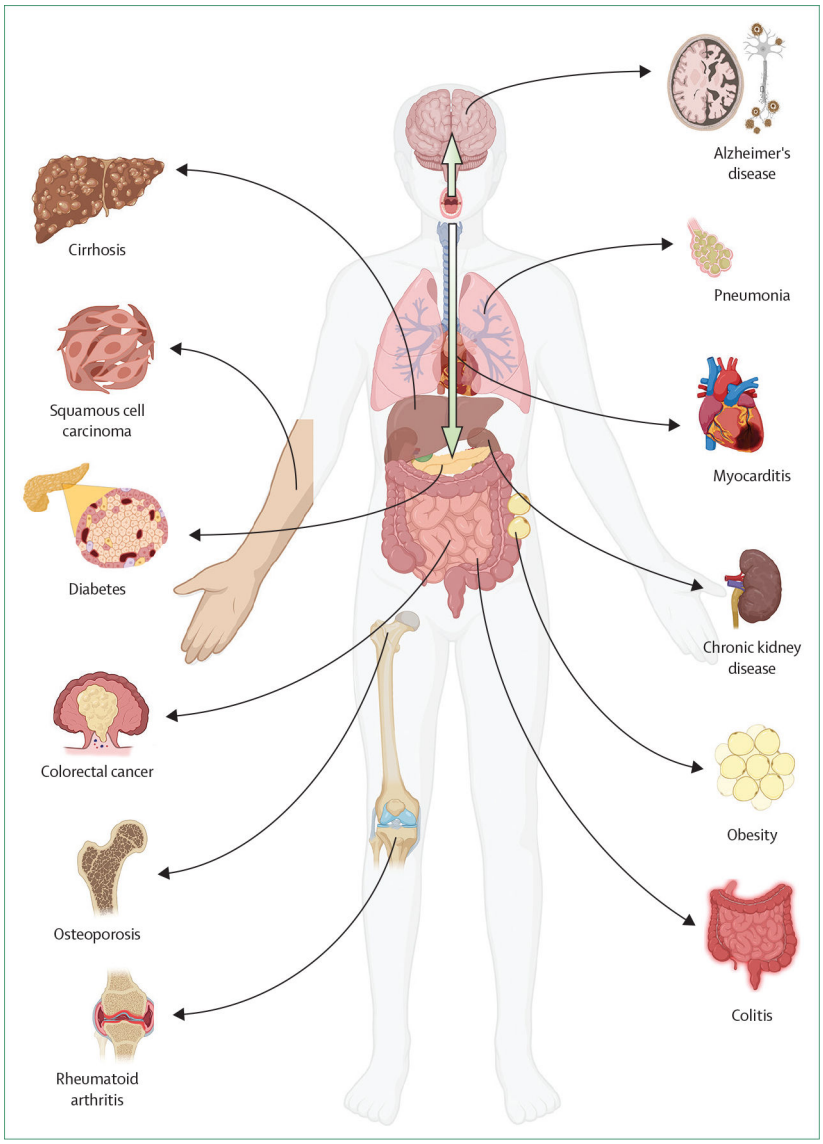

Figure 4: Periodontitis-associated systemic comorbidities
Figure created with BioRender.com.