



HAL
open science

Porphyromonas gingivalis, a Long-Range Pathogen: Systemic Impact and Therapeutic Implications

Hannah Mulhall, Olivier Huck, Salomon Amar

► **To cite this version:**

Hannah Mulhall, Olivier Huck, Salomon Amar. Porphyromonas gingivalis, a Long-Range Pathogen: Systemic Impact and Therapeutic Implications. *Microorganisms*, 2020, 8 (6), pp.869. 10.3390/microorganisms8060869 . hal-03886257

HAL Id: hal-03886257

<https://hal.science/hal-03886257v1>

Submitted on 6 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Review

Porphyromonas gingivalis, a Long-Range Pathogen: Systemic Impact and Therapeutic Implications

Hannah Mulhall¹, Olivier Huck^{2,3,4}  and Salomon Amar^{1,2,*}

¹ Department of Microbiology and Immunology, New York Medical College, Valhalla, NY 10595, USA; Hannah_Mulhall@student.nymc.edu

² Department of Pharmacology, New York Medical College, Valhalla, NY 10595, USA; Huck.Olivier@gmail.com

³ Faculté de Chirurgie-Dentaire, Université de Strasbourg, 8 rue Sainte-Elisabeth, 67000 Strasbourg, France

⁴ INSERM (French National Institute of Health and Medical Research), UMR 1260, Regenerative Nanomedicine, Fédération de Médecine Translationnelle de Strasbourg (FMTS), 67000 Strasbourg, France

* Correspondence: salomon_amar@nymc.edu

Received: 27 May 2020; Accepted: 5 June 2020; Published: 9 June 2020



Abstract: Periodontitis is an inflammatory disease associated with a dysbiosis of the oral flora characterized by a chronic sustained inflammation leading to destruction of tooth-supporting tissues. Over the last decade, an association between periodontitis and systemic disorders such as cardiovascular diseases, rheumatoid arthritis and obesity has been demonstrated. The role of periodontal pathogens, notably *Porphyromonas gingivalis* (*P. gingivalis*), in the onset or exacerbation of systemic diseases has been proposed. *P. gingivalis* expresses several virulence factors that promote its survival, spreading, and sustaining systemic inflammation. Recently, the impact of periodontitis on gut dysbiosis has also been suggested as a potential mechanism underlying the systemic influence of periodontitis. New therapeutic strategies for periodontitis and other dysbiotic conditions, including the use of beneficial microbes to restore healthy microbial flora, may pave the way to improved therapeutic outcomes and more thorough patient management.

Keywords: periodontitis; inflammation; systemic interactions; infection; dysbiosis; microbiome

1. Introduction

Periodontitis is an oral inflammatory disease of infectious origin affecting *periodontium*, characterized by gingival swelling and bleeding, periodontal pocket formation and clinical attachment loss, destruction of tooth-supporting tissue and ultimately to tooth loss [1,2]. Periodontitis is among the most common diseases worldwide, with its severe form affecting approximately 11% of the global population [3]. This disease represents a major public health issue as periodontitis has been correlated with decreased oral health and related quality of life [4]. Furthermore, an association with several systemic diseases such as cardiovascular diseases, diabetes and rheumatoid arthritis was established [5]. The oral microbiome is a highly complex ecosystem with thousands of microbial phylotypes detected [6], and its understanding presents a challenge. In the context of periodontal inflammation, the contribution of microbiome dysbiosis is under investigation due to the molecular mechanisms underlying this microbiome state being poorly understood.

Microbiome dysbiosis is characterized by an imbalance between microbial species and their environment. The imbalance seems to be driven by the subversion of host immunity due to keystone pathogens even when they are present in low abundance [7,8]. Typically, an inflammatory host response would lead to the clearance of pathogenic bacteria. However, in the case of periodontal disease, it promotes the growth of keystone pathogens due to gingival inflammatory exudate being

a rich source of nutrients [9]. Keystone pathogens, such as *Porphyromonas gingivalis* (*P. gingivalis*), facilitate the subversion of the host immune response through polymicrobial synergy allowing for the growth of both themselves and other dysbiotic species [10–12]. Polymicrobial synergy within the pathogenic oral biofilm is critical for the establishment and spread of periodontal disease. It has been demonstrated in vitro that there is a cooperative biofilm formation involving *Streptococcus gordonii*, *Fusobacterium nucleatum* (*F. nucleatum*) and *P. gingivalis* [12]. When cocultured, these bacteria elicited extensive changes on each other's biochemical signatures to support cohabitation within the biofilm [13]. During colonization, *F. nucleatum* triggers the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the host cells which provides a more favorable environment for *P. gingivalis* attachment [14]. Furthermore, this leads to the upregulation of virulence factor, mfa1 fimbriae, in both *F. nucleatum* and *P. gingivalis* preventing dendritic cell maturation allowing the disruption of the innate immune response [12].

P. gingivalis deploys an extensive arsenal of virulence factors such as lipopolysaccharide, proteases, fimbriae and a CRISPR-Cas system [8,15,16]; enabling it to modulate the host immune response to promote its survival through cellular colonization and spreading [17,18]. During the initial phase of infection, this bacterium manipulates the immune system through inhibition of cytokines and chemokines secretion [19,20]. Neutrophil homing to the gingival tissues is critical for maintaining homeostasis between the host and the microbiome. *P. gingivalis* creates a chemokine paralysis by degrading IL-8 through its secreted gingipain proteases and prevents IL-8 transcription through SerB, a haloacid dehalogenase (HAD) family serine phosphatase [21,22]. Furthermore, the ability of *P. gingivalis* to persist in the periodontal tissue after chemokine paralysis may depend to its ability to hijack the complement system, preventing its clearance from the oral cavity [11,23,24]. In addition to paralyzing the immune response, *P. gingivalis* also targets other periodontal cell types such as gingival epithelial cells, fibroblasts, periodontal ligament cells, and osseous cells, leading to the establishment of an inflammatory environment [17,18,25–27]. This hijacking of the host immune response hinders immune cell recruitment, allowing *P. gingivalis* to spread and colonize the periodontal pocket.

2. Distant Dissemination of *P. gingivalis*

Over the last decade, there has been increased interest on the links between periodontitis and systemic diseases [5]. Among them, an association has been demonstrated with major chronic diseases such as cardiovascular diseases [28], diabetes [29], metabolic syndrome [30], rheumatoid arthritis [31] and more recently obesity [32] (Figure 1). Interestingly, periodontitis has been documented as contributing to the risk of all-cause mortality in an older European population (subjects 60–70 years of age; hazard ratio = 1.57 (1.04–2.36) after adjustment for confounding variables) [33]. Therefore, the systemic effects of oral pathogens and the role they play in chronic diseases has become a major research focus.

Among the oral bacteria that exhibit systemic effects, *P. gingivalis* has stood out. It has been detected in several diseased tissues and organs in both humans and animal models. The translocation of *P. gingivalis* to the distant tissues such as the liver or joint after oral administration [34,35] and its detection in brains of patients with Alzheimer's disease [36] has led to an increased interest in determining its role in chronic inflammatory diseases.

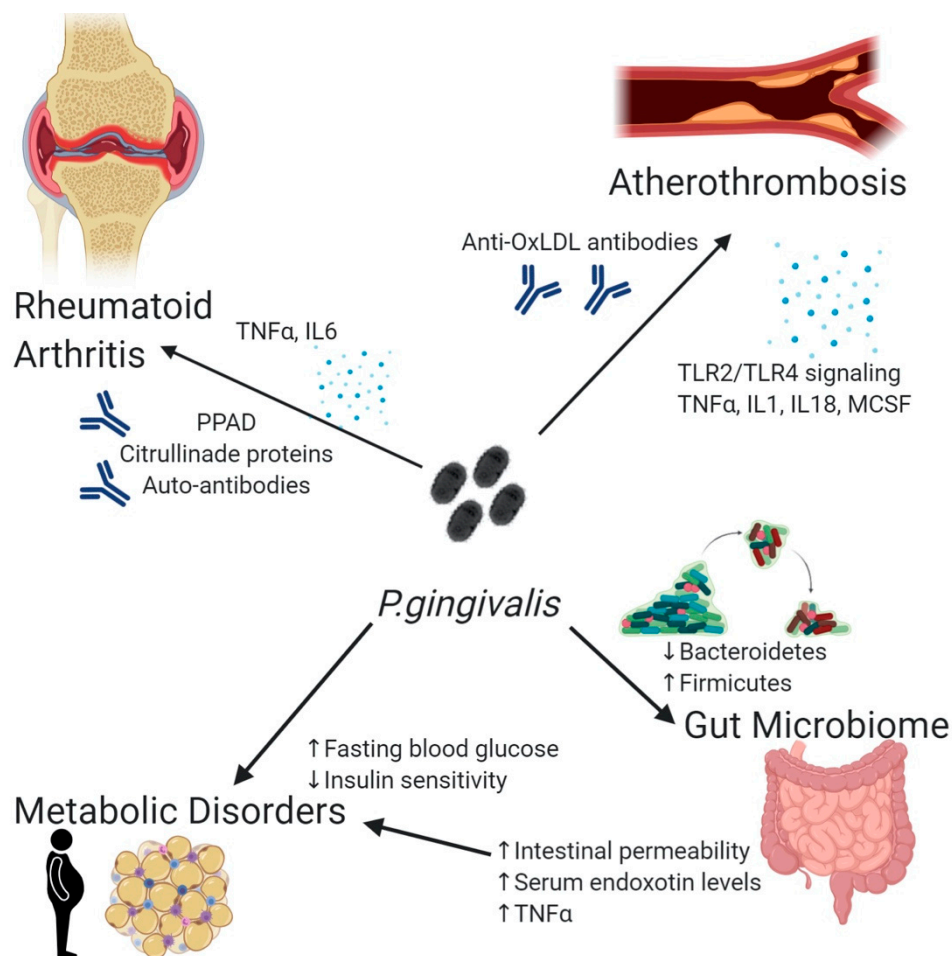


Figure 1. *Porphyromonas gingivalis* influences the development of multiple chronic inflammatory conditions. Through the cross-reactive antibodies (atherothrombosis, rheumatoid arthritis), increased levels of systemic inflammation (atherothrombosis, rheumatoid arthritis, gut microbiome dysbiosis, metabolic disorders), as well as overall microbiome dysbiosis. (↑ = increase ↓ = decrease).

3. Pathogenicity of *P. gingivalis*: The Case of Atherothrombosis

Chronic infection has been identified as a potential contributor to the development of atherosclerotic lesions independent of classical risk factors such as unfavorable lipid profile [37,38]. *Chlamydia pneumoniae*, *Helicobacter pylori*, *P. gingivalis* and certain viruses have been detected within atheromatous plaque [39–41]. However, their impact remains under investigation. Several periodontal pathogens have been detected in both atherosclerotic plaque and healthy vessels [41,42]. *P. gingivalis* is among the most commonly found organism in these studies due to its ability to persist within vascular tissue through cell-to-cell transmission [43].

The severity of periodontitis in experimental models has been shown to correlate with the magnitude of the systemic inflammation as well as atheromatous plaque formation. Oral administration of *P. gingivalis* has been reported to accelerate the development of atherosclerosis in apolipoprotein E knock out (ApoE^{-/-}) mice [38,44,45]. In the experimental models of periodontitis, it has been demonstrated that there is an increased systemic inflammation, potentially contributing to vascular lesion development [46,47]. Signaling through TLR-2 and TLR-4 is critical for the development of periodontitis, as well as atherosclerotic plaque progression [48]. It has been demonstrated that *P. gingivalis* is able to activate these membrane receptors on the endothelial level [49,50] triggering the secretion of cytokines such as TNF- α , IL-1, IL-18 and M-CSF [51] thus, contributing to a persistent inflammation. Furthermore, in these mice, *P. gingivalis* DNA can be found in the aortic tissue along

with an abundance of activated macrophages [44,45]. Interestingly, when nonsurgical periodontal therapy is performed in these models, there is a reduction in systemic inflammation as well as aortic inflammation supporting the causative role oral microbiome dysbiosis [52].

Oxidized low density lipoproteins (OxLDLs) are believed to initiate the immunological response found in atherosclerosis [53]. It has been demonstrated in patients with stable coronary artery disease, as well as acute coronary disease, that antibodies directed against key virulence factors of *P. gingivalis* can cross-react with OxLDLs, malondialdehyde-modified low-density lipoprotein (MDA-LDL) and to malondialdehyde acetaldehyde-modified low-density lipoprotein (MAA-LDL) [54]. In vitro, the synergic effects between risk factors have also been observed. Indeed, *P. gingivalis*-induced effects can be influenced by the cellular environment and other proinflammatory triggers, such as oxidized low-density lipoproteins, (Ox-LDL) [55] highlighting the fact that vascular inflammation could arise from different mechanisms and insults. The antibody cross-reaction between bacterial components and host molecules may also contribute to the inflammatory environment in the atherosclerotic plaque. In mouse models, immunization with *P. gingivalis* or its gingipain, Rgp44, seems to display athero-protective effects in the modulation of plaque size, and anti-inflammatory cytokines IL-10 and IL-5 [54].

Based on the cumulative evidence strengthening the role of bacterial infection in atherosclerosis, several clinical trials have been conducted assessing the impact of antibiotic administration on atherosclerosis-related parameters in patients with stable coronary artery disease (WIZARD, ACES, CLARICOR), acute coronary syndrome (PROVE-IT-TIMI) and peripheral artery disease (PROVIDENCE-1) [56–60]. However, none of these trials demonstrated long term benefit of such a therapeutic strategy. These results might be explained by the fact that 1. antibiotics never penetrate a biofilm unless mechanically disrupted; 2. antibiotics must be able to address host cell invasion by pathogens; 3. the poorly designed studies focus mainly on late stages of atherothrombosis, reducing the ability to detect a benefit of such an approach [61]. Future trials testing the effect of antibiotics on earlier stage disease might be worth consideration.

4. *P. gingivalis* and Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that primarily affects the joints, however, the condition can damage a wide variety of body systems including the skin, eyes, lungs, heart and blood vessels [62]. The notion that RA had an infectious origin is not a new one. Since the early 19th century, investigators have claimed to identify different bacteria in RA synovial fluid and tissue. Although these results were not reproducible, the evidence supported the theory that RA was a result of microbial action either within the joint or systemically [63]. The association between periodontal disease and RA has long been established [64]. Initially, it was thought that the alveolar bone destruction and gingival inflammation was part of the same RA-induced damage. It was not until recently that periodontitis was seen more as a cause than a consequence of RA. Like periodontitis, the tissue damage seen in RA is due to a host driven inflammation [65,66]. The cytokine signature of each disease is similar with an increased expression of proinflammatory cytokines, TNF- α and IL-6. In murine models of experimental arthritis, it was found that there is an increase in the serum levels of these inflammatory mediators following oral administration of periodontal pathogens, supporting their role in exacerbating the local and systemic inflammation associated with RA [67–69]. Additionally, auto-antibodies such as rheumatoid factor and anticollagen antibodies common to RA are often found in diseased periodontal tissues [70,71]. Specific periodontal pathogens have even been identified as risk factors for the development of RA, and *P. gingivalis* in particular has received a lot of attention. *P. gingivalis* secretes a peptidylarginine deiminase (PAD)-like enzyme (PPAD), which can contribute to the generation of citrullinated proteins, a major target of autoantibodies in RA [72,73]. PPAD is secreted in a soluble form and in association with the outer membrane vesicles of *P. gingivalis* [74]. As a major virulence factor, PPAD helps to maintain the presence of *P. gingivalis* in the mouth by preventing neutrophil function as well as the production of ammonia [75–77]. Clinical isolates of *P. gingivalis*

have been shown to be highly enriched in citrullinated proteins due to the functioning of PPAD as well as its gingipain Rgp [73,78]. In murine models of collagen-induced arthritis, inoculation with *P. gingivalis* lead to an increase in citrullinated peptides as well as an increased expression of proteins targeted for citrullination [78]. The production of bacterial and host citrullinated proteins by PPAD may further exacerbate the loss of tolerance to citrullinated autoantigens in RA. In murine models of collagen-induced arthritis PPAD-null mutants, *P. gingivalis* does not elicit the same level of inflammation or autoantibodies to collagen type II, highlighting its potential for therapeutic targeting [73]. In addition to autoreactive antibodies, patients with RA often have high levels of antibodies to *P. gingivalis* gingipain domains [79]. A majority of the antigingipain antibodies target the hemagglutinin (HA2-4) as well as the catalytic domains [80]. Interestingly, in the murine model of collagen-induced arthritis, rats that received a pretreatment vaccination of the catalytic domain of RgpA had less severe cartilage erosive changes when compared to controls. Furthermore, rats that received the catalytic domain of RgpA demonstrated a reduction in inflammatory mediators (IL-1b and TNF- α) both at the mRNA and protein level in the synovial tissues [79].

It is difficult to clearly define periodontitis and periodontal pathogens as microbial cause of RA, given 11% of the global adult population present periodontitis and RA affects only 0.5 to 1% [3,81]. However, there is overwhelming evidence to support that periodontal pathogens, specifically *P. gingivalis*, play a role in the progression of the disease by allowing for the accumulation of inflammatory cytokines and autoreactive antibodies, leading to the tissue destruction associated with RA [69,82–84]. Furthermore, it has been demonstrated in numerous animal models of experimental arthritis that arthritis can be treated by targeting *P. gingivalis* and its numerous virulence factors, supporting the need for further investigation into the effects of nonsurgical periodontal treatment and the progression of RA in human trials.

5. Impact of *P. gingivalis* on Obesity, Metabolism, and Gut Microbiota Homeostasis

The amount of data illustrating a relationship between obesity and periodontitis [85] has led to interest in the potential role played by *P. gingivalis* on both sustained inflammation in adipose tissue and gut microbiome-associated changes. It has been suggested that bacterial insult may contribute to obesity-related chronic inflammation and oxidative stress [86]. Endotoxemia characterized by high plasma level of bacterial lipopolysaccharides (LPS) has been shown to stimulate adipocyte proliferation and inflammation in adipose tissue [87]. Interestingly, infection of macrophages by *P. gingivalis* induced a switch in macrophage polarization leading to the inhibition of M1 phenotype, illustrating an alteration of immune response with effects on a cascade of pathways associated with immune cell proliferation and angiogenesis. These effects are potential causes of the delay in the response to infection observed in obese individuals [88]. However, it should be mentioned that a sole bacterium cannot cause metabolic endotoxemia and that the establishment of the low-grade inflammation is the result of a complex process that involves the whole microbiota, including butyrate-producing bacteria, mucin-degrading bacteria and LPS-containing bacteria such as *P. gingivalis* [87,89–91].

The gut microbiome has recently come to be viewed as an organ system in its own right [92]. It is the most diverse commensal ecosystem in the human body that continues to evolve throughout the human lifespan [93]. Microbes residing in the gut are considered key contributors to host metabolism as they interact with virtually all human cells and induce significant changes in host metabolism [89]. Metabolic disorders, such as obesity, are associated with shifts in the microbiota at the phylum level, especially in the Firmicutes/Bacteroidetes ratio [94]. Saliva is an important transporter of oral bacteria to the gut as daily saliva production is approximately 0.6 L [95]. Clinical trials have demonstrated that bacterial counts of periodontal pathogens in saliva (*Campylobacter rectus*, *F. nucleatum*, *P. gingivalis*, *Prevotella intermedia* and *Tannerella forsythia*) were increased with the severity of periodontal disease (gingivitis/periodontitis) [96]. It has been hypothesized that swallowed oral pathogens can lead to disturbances in the gut microbiota causing metabolic endotoxemia and metabolic disorders [97]. Patients with chronic periodontitis have been shown to have less diversity in their

gut microbiomes [98]. Several studies have investigated the influence of *P. gingivalis* oral gavage on the gut microbiome, mostly in animal models. All studies indicate a significant modification of gut microbiome composition after *P. gingivalis* oral administration [99,100]. In C57BL/6 mice infected with *P. gingivalis* strain W83, Kato et al. showed that the proportion of Bacteroidetes was significantly reduced compared to sham-administered mice, indicating a dysbiosis of the gut microbiome. Interestingly, the proportions of other genera such as *Lactobacillus* and *Desulfovibrio* were also affected by *P. gingivalis* administration [99]. Due to the changes in the gut microbiome, *P. gingivalis* administration leads to increased systemic inflammation, endotoxin levels, and intestinal permeability, even after a single exposure [100]. The increased systemic inflammation contributes to the changes in gene expression profiles of epididymal adipose tissue, increasing proinflammatory genes while decreasing insulin sensitivity [97], as well as changes in expression of genes associated with glucose and lipid metabolism [99,101]. However, the limitations associated with the use of mouse models should be mentioned. Mouse models lack some human-specific gut bacteria and proportion of bacterial phyla is different compared to humans. Furthermore, the immune responses also differ [102]. Altogether, these limitations indicate the need of human studies. In humans, the Human Microbiome Project demonstrated that several genera, including *Bacteroides*, *Faecalibacterium*, *Parabacteroides*, *Eubacterium*, *Alistipes*, *Dialister*, *Streptococcus*, *Prevotella*, *Rosburia*, *Coprococcus*, *Veillonella* and *Oscilibacter* could be detected in both the oral cavity and stool in more than 45% of the included patients [103], highlighting a potential role for oral bacteria in the disruption of the gut microbiome. It was therefore hypothesized that saliva is a key driver of microbial composition in the habitats above the stomach. However, the role of the continuous epithelial lining of the upper gastrointestinal mucosal surfaces has also been suggested [103].

Obesity is also associated with metabolic alterations such as glucose homeostasis including glucose intolerance, diabetes and insulin resistance [104], all of which are associated with low-grade inflammation. Metabolic endotoxemia induced by LPS has been associated with insulin resistance [105]. Interestingly, it was demonstrated that mice fed a high-fat diet and treated with antibiotics exhibited reduced inflammation, insulin resistance and fat mass gain, emphasizing a role of the gut microbiota [106]. In the context of periodontitis and experimental periodontitis induced by *P. gingivalis*, obese animals exhibited greater periodontal bone loss than in lean animals; a process attributed to a severe immune dysfunction [88,107–109]. Experimental periodontitis induced by multispecies (*P. gingivalis*, *F. nucleatum*, *P. intermedia*) oral gavage was associated with increased insulin resistance [110]. This modulation of the insulin resistance was linked to the recruitment of cells involved in the adaptive immune response, and a decrease in antibodies against *P. gingivalis* was associated with impaired glucose metabolism [110].

Conventional periodontal treatments including scaling and root planning with adjuvant therapies such as topical antibiotics have been demonstrated to alleviate some of the symptoms of metabolic disorders. In fact, such treatments have led to a reduction in serum glucose and glycated hemoglobin, insulin resistance, and fasting glucose levels [111–113]. There is little understanding of the impact of periodontal treatment on the composition of the gut microbiome. Due to the ability of periodontal treatment to change the serum metabolome, the effects on the composition of the microbiome should be investigated.

6. Clinical Implications

Periodontal treatment aims to achieve resolution of gingival inflammation and a decrease in the pathogenic bacterial load [114]. It includes nonsurgical periodontal therapy consisting of oral hygiene instructions, scaling and root planning of affected teeth. In cases of severe lesions, anti-infective treatment may be used as an adjunctive to mechanical treatment. Accordingly, antiseptics, antibiotics, and local anti-infective treatments such as photodynamic therapy have been proposed to reduce the need for additional surgical treatment [115–117]. Such therapeutic approaches are effective in most clinical situations. However, in some patients, refractory lesions and recurrence leading ultimately to

tooth loss could be observed [118,119], emphasizing the need for pharmacological approaches such as antibiotics.

Recently, the modulation of the biofilm composition has also been proposed as a therapeutic approach through the administration of beneficial microbes [120,121]. In this aspect, *Lactobacillus* strains, especially *L.reuteri*, were the most evaluated in human clinical settings. They showed a significant impact with a reduction in clinical attachment loss (-0.42 mm, $p = 0.002$) and gingival inflammation, as well as a significant reduction in bleeding on probing (-14.66% , $p = 0.03$) [121]. The mechanisms associated with oral administration of probiotics at the periodontal level are not fully elucidated yet. However, probiotic treatment has demonstrated an inhibitory effect towards bacteria present within periodontal biofilms such as *Streptococcus mutans*, *Streptococcus gordonii*, *Tannerella forsythia* and *Actinomyces naeslundii*. Interestingly, it was also demonstrated that the antimicrobial activity of *L. reuteri* was not associated with its viability, as even heat-killed bacteria or culture supernatant were effective, indicating a likely role for substances produced by the beneficial bacteria such as reutericyclin [122]. Interestingly, in rodent models, the restoration of a healthy gut flora concomitant with administration of probiotics such as *L. plantarum* was associated to cardioprotective effects, improved cardiac function and decreased inflammatory markers [123].

The gut symbiont *Akkermansia muciniphila* (*A. muciniphila*) has been evaluated as a new potential therapeutic tool for periodontitis. *A. muciniphila* has attracted growing interest due to its host-beneficial properties. In several rodent models, supplementation with *A. muciniphila* reduces obesity, insulin resistance, glucose intolerance, steatosis and gut permeability [124–126]. Such properties suggest *A. muciniphila* as a next-generation probiotic [127]. Furthermore, there has been additional focus on one of its membrane proteins, Amuc_1100 [128], demonstrating its ability to recapitulate the effect induced by live bacteria. Amuc_1100 interacts with TLR- 2 and -4 resulting in the improvement of gut barrier function and anti-inflammatory IL-10 secretion in mouse models [125,129]. In humans, a recent proof-of-concept exploratory study shows that the supplementation with *A. muciniphila* was safe and well tolerated. Most importantly, the administration of this gut commensal administration in human obese volunteers, notably in pasteurized form, contributed to body weight reduction in comparison with placebo treated patients, but also reduced the level of markers associated with liver dysfunction and inflammation such as fasting plasma insulin, total cholesterol and γ GT [130]. In the context of periodontitis, administration of *A.muciniphila* in a murine model of experimental periodontitis was associated with improved periodontal healing [120]. This effect was associated with a modulation of *P. gingivalis* virulence by *A. muciniphila* in cocultures. As observed for *L. reuteri*, some studies showed the role of a secreted bacterial byproduct, Amuc_1100 in the anti-inflammatory properties [125]. The impact of the oral administration of *A. muciniphila* on the gut microbiome was also observed and associated with changes in the ratio of Firmicutes/Bacteroidetes, highlighting a potential influence of gut ecology on systemic inflammation levels [120].

7. Conclusions

The detrimental effect of periodontitis on other major systemic diseases with high social and financial consequences has been demonstrated. Modulation of the microbiome has emerged as an exciting potential treatment that could pave the way for a new approach to managing periodontal diseases, as well as their systemic effects. New research is needed to establish the molecular mechanisms involved, and to elucidate effects related to both local antimicrobial properties and systemic anti-inflammatory effects associated with the transition from a dysbiotic to a healthy gut microbiome. Additionally, studies are needed to determine the most effective probiotic organisms, strains, dosage, and routes of administration necessary to achieve optimal outcomes in each respective disease. With further research into the effects of modulation of the oral microbiome on systemic disease, promising new treatments for these chronic inflammatory diseases will emerge.

Author Contributions: Conceptualization, O.H. and S.A.; methodology, O.H, S.A.; data curation, H.M. and O.H.; writing—original draft preparation, H.M., O.H. and S.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by NIH/NIDCR, grant #R01DE014079 and NIH/NHLBI grant #R01HL076801.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Caton, J.G.; Armitage, G.; Berglundh, T.; Chapple, I.L.C.; Jepsen, S.; Kornman, K.S.; Mealey, B.L.; Papapanou, P.N.; Sanz, M.; Tonetti, M.S. A new classification scheme for periodontal and peri-implant diseases and conditions—Introduction and key changes from the 1999 classification. *J. Periodontol.* **2018**, *89*, S1–S8. [[CrossRef](#)] [[PubMed](#)]
2. Kinane, D.F.; Stathopoulou, P.G.; Papapanou, P.N. Periodontal diseases. *Nat. Rev. Dis. Primer* **2017**, *3*, 17038. [[CrossRef](#)] [[PubMed](#)]
3. Kassebaum, N.J.; Bernabe, E.; Dahiya, M.; Bhandari, B.; Murray, C.J.L.; Marcenes, W. Global Burden of Severe Periodontitis in 1990–2010: A Systematic Review and Meta-regression. *J. Dent. Res.* **2014**, *93*, 1045–1053. [[CrossRef](#)] [[PubMed](#)]
4. Sulaiman, L.; Saub, R.; Baharuddin, N.A.; Safii, S.H.; Gopal Krishna, V.; Bartold, P.M.; Vaithilingam, R.D. Impact of Severe Chronic Periodontitis on Oral Health-related Quality of Life. *Oral Health Prev. Dent.* **2019**, *17*, 365–373. [[CrossRef](#)] [[PubMed](#)]
5. Linden, G.J.; Lyons, A.; Scannapieco, F.A. Periodontal systemic associations: Review of the evidence. *J. Clin. Periodontol.* **2013**, *40*, 8–19. [[CrossRef](#)]
6. Keijsers, B.J.F.; Zaura, E.; Huse, S.M.; van der Vossen, J.M.B.M.; Schuren, F.H.J.; Montijn, R.C.; ten Cate, J.M.; Crielaard, W. Pyrosequencing analysis of the oral microflora of healthy adults. *J. Dent. Res.* **2008**, *87*, 1016–1020. [[CrossRef](#)]
7. Lamont, R.J.; Koo, H.; Hajishengallis, G. The oral microbiota: Dynamic communities and host interactions. *Nat. Rev. Microbiol.* **2018**, *16*, 745–759. [[CrossRef](#)]
8. Zenobia, C.; Hajishengallis, G. Porphyromonas gingivalis virulence factors involved in subversion of leukocytes and microbial dysbiosis. *Virulence* **2015**, *6*, 236–243. [[CrossRef](#)]
9. Darveau, R.P. Periodontitis: A polymicrobial disruption of host homeostasis. *Nat. Rev. Microbiol.* **2010**, *8*, 481–490. [[CrossRef](#)]
10. Zenobia, C.; Hasturk, H.; Nguyen, D.; Dyke, T.E.V.; Kantarci, A.; Darveau, R.P. Porphyromonas gingivalis Lipid A Phosphatase Activity Is Critical for Colonization and Increasing the Commensal Load in the Rabbit Ligature Model. *Infect. Immun.* **2014**, *82*, 650–659. [[CrossRef](#)]
11. Hajishengallis, G.; Liang, S.; Payne, M.A.; Hashim, A.; Jotwani, R.; Eskan, M.A.; McIntosh, M.L.; Alsam, A.; Kirkwood, K.L.; Lambris, J.D.; et al. Low-Abundance Biofilm Species Orchestrates Inflammatory Periodontal Disease through the Commensal Microbiota and Complement. *Cell Host Microbe* **2011**, *10*, 497–506. [[CrossRef](#)] [[PubMed](#)]
12. El-Awady, A.; de Sousa Rabelo, M.; Meghil, M.M.; Rajendran, M.; Elashiry, M.; Stadler, A.F.; Foz, A.M.; Susin, C.; Romito, G.A.; Arce, R.M.; et al. Polymicrobial synergy within oral biofilm promotes invasion of dendritic cells and survival of consortia members. *Npj Biofilms Microbiomes* **2019**, *5*, 1–12. [[CrossRef](#)] [[PubMed](#)]
13. Hendrickson, E.L.; Wang, T.; Dickinson, B.C.; Whitmore, S.E.; Wright, C.J.; Lamont, R.J.; Hackett, M. Proteomics of *Streptococcus gordonii* within a model developing oral microbial community. *BMC Microbiol.* **2012**, *12*, 211. [[CrossRef](#)]
14. Ahn, S.H.; Song, J.-E.; Kim, S.; Cho, S.-H.; Lim, Y.K.; Kook, J.-K.; Kook, M.-S.; Lee, T.-H. NOX1/2 activation in human gingival fibroblasts by *Fusobacterium nucleatum* facilitates attachment of *Porphyromonas gingivalis*. *Arch. Microbiol.* **2016**, *198*, 573–583. [[CrossRef](#)] [[PubMed](#)]
15. Chen, T.; Olsen, I. *Porphyromonas gingivalis* and its CRISPR-Cas system. *J. Oral Microbiol.* **2019**, *11*, 1638196. [[CrossRef](#)] [[PubMed](#)]

16. Cugini, C.; Klepac-Ceraj, V.; Rackaityte, E.; Riggs, J.E.; Davey, M.E. *Porphyromonas gingivalis*: Keeping the pathos out of the biont. *J. Oral Microbiol.* **2013**, *5*, 19804. [[CrossRef](#)]
17. Bugueno, I.M.; Batool, F.; Korah, L.; Benkirane-Jessel, N.; Huck, O. *Porphyromonas gingivalis* Differentially Modulates Apoptosome Apoptotic Peptidase Activating Factor 1 in Epithelial Cells and Fibroblasts. *AJPA* **2018**, *188*, 404–416. [[CrossRef](#)]
18. Bugueno, I.M.; Batool, F.; Keller, L.; Kuchler-Bopp, S.; Benkirane-Jessel, N.; Huck, O. *Porphyromonas gingivalis* bypasses epithelial barrier and modulates fibroblastic inflammatory response in an in vitro 3D spheroid model. *Sci. Rep.* **2018**, *8*, 30. [[CrossRef](#)]
19. Huck, O.; Elkaim, R.; Davideau, J.-L.; Tenenbaum, H. *Porphyromonas gingivalis*-impaired innate immune response via NLRP3 proteolysis in endothelial cells. *Innate Immun.* **2014**, *21*, 1–8. [[CrossRef](#)]
20. Yu, S.; Ding, L.; Liang, D.; Luo, L. *Porphyromonas gingivalis* inhibits M2 activation of macrophages by suppressing α -ketoglutarate production in mice. *Mol. Oral Microbiol.* **2018**, *33*, 388–395. [[CrossRef](#)]
21. Sochalska, M.; Potempa, J. Manipulation of Neutrophils by *Porphyromonas gingivalis* in the Development of Periodontitis. *Front. Cell. Infect. Microbiol.* **2017**, *7*, 197. [[CrossRef](#)]
22. Takeuchi, H.; Hirano, T.; Whitmore, S.E.; Morisaki, I.; Amano, A.; Lamont, R.J. The Serine Phosphatase SerB of *Porphyromonas gingivalis* Suppresses IL-8 Production by Dephosphorylation of NF- κ B RelA/p65. *PLoS Pathog.* **2013**, *9*, e1003326. [[CrossRef](#)] [[PubMed](#)]
23. Maekawa, T.; Krauss, J.L.; Abe, T.; Jotwani, R.; Triantafilou, M.; Triantafilou, K.; Hashim, A.; Hoch, S.; Curtis, M.A.; Nussbaum, G.; et al. *Porphyromonas gingivalis* manipulates complement and TLR signaling to uncouple bacterial clearance from inflammation and promote dysbiosis. *Cell Host Microbe* **2014**, *15*, 768–778. [[CrossRef](#)] [[PubMed](#)]
24. Popadiak, K.; Potempa, J.; Riesbeck, K.; Blom, A.M. Biphasic Effect of Gingipains from *Porphyromonas gingivalis* on the Human Complement System. *J. Immunol.* **2007**, *178*, 7242–7250. [[CrossRef](#)] [[PubMed](#)]
25. Han, E.-C.; Choi, S.-Y.; Lee, Y.; Park, J.-W.; Hong, S.-H.; Lee, H.-J. Extracellular RNAs in periodontopathogenic outer membrane vesicles promote TNF- α production in human macrophages and cross the blood-brain barrier in mice. *FASEB J.* **2019**. [[CrossRef](#)]
26. Lapérine, O.; Cloitre, A.; Caillon, J.; Huck, O.; Bugueno, I.M.; Pilet, P.; Sourice, S.; Le Tilly, E.; Palmer, G.; Davideau, J.-L.; et al. Interleukin-33 and RANK-L Interplay in the Alveolar Bone Loss Associated to Periodontitis. *PLoS ONE* **2016**, *11*, e0168080-17. [[CrossRef](#)]
27. Yuan, H.; Gupte, R.; Zelkha, S.; Amar, S. Receptor activator of nuclear factor kappa B ligand antagonists inhibit tissue inflammation and bone loss in experimental periodontitis. *J. Clin. Periodontol.* **2011**, *38*, 1029–1036. [[CrossRef](#)]
28. Huck, O.; Saadi-Thiers, K.; Tenenbaum, H.; Davideau, J.-L.; Romagna, C.; Laurent, Y.; Cottin, Y.; Roul, J.G. Evaluating periodontal risk for patients at risk of or suffering from atherosclerosis: Recent biological hypotheses and therapeutic consequences. *Arch. Cardiovasc. Dis.* **2017**, 1–7. [[CrossRef](#)]
29. Preshaw, P.M.; Alba, A.L.; Herrera, D.; Jepsen, S.; Konstantinidis, A.; Makrilakis, K.; Taylor, R. Periodontitis and diabetes: A two-way relationship. *Diabetologia* **2012**, *55*, 21–31. [[CrossRef](#)]
30. Nibali, L.; Tatarakis, N.; Needleman, I.; Tu, Y.-K.; D’Aiuto, F.; Rizzo, M.; Donos, N. Association between Metabolic Syndrome and Periodontitis: A Systematic Review and Meta-analysis. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 913–920. [[CrossRef](#)]
31. Chou, Y.-Y.; Lai, K.-L.; Chen, D.-Y.; Lin, C.-H.; Chen, H.-H. Rheumatoid Arthritis Risk Associated with Periodontitis Exposure: A Nationwide, Population-Based Cohort Study. *PLoS ONE* **2015**, *10*, e0139693. [[CrossRef](#)] [[PubMed](#)]
32. Nascimento, G.G.; Peres, M.A.; Mittinty, M.N.; Peres, K.G.; Do, L.G.; Horta, B.L.; Gigante, D.P.; Corrêa, M.B.; Demarco, F.F. Diet-Induced Overweight and Obesity and Periodontitis Risk: An Application of the Parametric G-Formula in the 1982 Pelotas Birth Cohort. *Am. J. Epidemiol.* **2017**, *185*, 442–451. [[CrossRef](#)] [[PubMed](#)]
33. Linden, G.J.; Linden, K.; Yarnell, J.; Evans, A.; Kee, F.; Patterson, C.C. All-cause mortality and periodontitis in 60–70-year-old men: A prospective cohort study. *J. Clin. Periodontol.* **2012**, *39*, 940–946. [[CrossRef](#)] [[PubMed](#)]
34. Ishikawa, M.; Yoshida, K.; Okamura, H.; Ochiai, K.; Takamura, H.; Fujiwara, N.; Ozaki, K. Oral *Porphyromonas gingivalis* Translocates to the Liver and Regulates Hepatic Glycogen Synthesis through the Akt/GSK-3 β Signaling Pathway. *Biochim. Biophys. Acta* **2013**, *1832*, 2035–2043. [[CrossRef](#)] [[PubMed](#)]

35. Jeong, S.H.; Nam, Y.; Jung, H.; Kim, J.; Rim, Y.A.; Park, N.; Lee, K.; Choi, S.; Jang, Y.; Kim, Y.; et al. Interrupting Oral Infection of *Porphyromons gingivalis* with anti-FimA Antibody Attenuates Bacterial Dissemination to the Arthritic Joint and Improves Experimental Arthritis. *Exp. Mol. Med.* **2018**, *50*, 460. [[CrossRef](#)] [[PubMed](#)]
36. Panza, F.; Lozupone, M.; Solfrizzi, V.; Watling, M.; Imbimbo, B.P. Time to test antibacterial therapy in Alzheimer's disease. *Brain* **2019**, *142*, 2905–2929. [[CrossRef](#)]
37. Rosenfeld, M.E.; Campbell, L.A. Pathogens and atherosclerosis: Update on the potential contribution of multiple infectious organisms to the pathogenesis of atherosclerosis. *Thromb. Haemost.* **2011**, *106*, 858–867. [[CrossRef](#)] [[PubMed](#)]
38. Li, L.; Messas, E.; Batista, E.L.; Levine, R.A.; Amar, S. *Porphyromonas gingivalis* infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. *Circulation* **2002**, *105*, 861–867.
39. Sessa, R.; Di Pietro, M.; Schiavoni, G.; Petrucca, A.; Cipriani, P.; Zagaglia, C.; Nicoletti, M.; Santino, I.; del Piano, M. Measurement of Chlamydia pneumoniae bacterial load in peripheral blood mononuclear cells may be helpful to assess the state of chlamydial infection in patients with carotid atherosclerotic disease. *Atherosclerosis* **2007**, *195*, 224–230. [[CrossRef](#)]
40. Izadi, M.; Fazel, M.; Sharubandi, S.H.; Saadat, S.H.; Farahani, M.M.; Nasser, M.H.; Dabiri, H.; Safi-Aryan, R.; Esfahani, A.A.; Ahmadi, A.; et al. Helicobacter Species in the Atherosclerotic Plaques of Patients with Coronary Artery Disease. *Cardiovasc Pathol.* **2012**, *21*, 307–311. [[CrossRef](#)]
41. Elkaim, R.; Dahan, M.; Kocgozlu, L.; Werner, S.; Kanter, D.; Kretz, J.G.; Tenenbaum, H. Prevalence of periodontal pathogens in subgingival lesions, atherosclerotic plaques and healthy blood vessels: A preliminary study. *J. Periodontol.* **2008**, *43*, 224–231. [[CrossRef](#)] [[PubMed](#)]
42. Rangé, H.; Labreuche, J.; Louedec, L.; Rondeau, P.; Planesse, C.; Sebbag, U.; Bourdon, E.; Michel, J.-B.; Bouchard, P.; Meilhac, O. Periodontal bacteria in human carotid atherothrombosis as a potential trigger for neutrophil activation. *Atherosclerosis* **2014**, *236*, 448–455. [[CrossRef](#)] [[PubMed](#)]
43. Li, L.; Michel, R.; Cohen, J.; Decarlo, A.; Kozarov, E. Intracellular survival and vascular cell-to-cell transmission of *Porphyromonas gingivalis*. *BMC Microbiol.* **2008**, *8*, 26. [[CrossRef](#)] [[PubMed](#)]
44. Suh, J.S.; Kim, S.; Boström, K.I.; Wang, C.-Y.; Kim, R.H.; Park, N.-H. Periodontitis-induced systemic inflammation exacerbates atherosclerosis partly via endothelial–mesenchymal transition in mice. *Int. J. Oral Sci.* **2019**, *11*, 1–12. [[CrossRef](#)] [[PubMed](#)]
45. Lalla, E.; Lamster, I.B.; Hofmann, M.A.; Bucciarelli, L.; Jerud, A.P.; Tucker, S.; Lu, Y.; Papapanou, P.N.; Schmidt, A.M. Oral Infection With a Periodontal Pathogen Accelerates Early Atherosclerosis in Apolipoprotein E–Null Mice. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 1405–1411. [[CrossRef](#)] [[PubMed](#)]
46. Saadi-Thiers, K.; Huck, O.; Simonis, P.; Tilly, P.; Fabre, J.-E.; Tenenbaum, H.; Davideau, J.-L. Periodontal and systemic responses in various mice models of experimental periodontitis: Respective roles of inflammation duration and *Porphyromonas gingivalis* infection. *J. Periodontol.* **2013**, *84*, 396–406. [[CrossRef](#)]
47. Chi, H.; Messas, E.; Levine, R.A.; Graves, D.T.; Amar, S. Interleukin-1 Receptor Signaling Mediates Atherosclerosis Associated with Bacterial Exposure and/or a High-Fat Diet in a Murine Apolipoprotein E Heterozygote Model. *Circulation* **2004**, *110*, 1678–1685. [[CrossRef](#)]
48. Chukkapalli, S.S.; Ambadapadi, S.; Varkoly, K.; Jiron, J.; Aguirre, J.I.; Bhattacharyya, I.; Morel, L.M.; Lucas, A.R.; Kesavalu, L. Impaired innate immune signaling due to combined Toll-like receptor 2 and 4 deficiency affects both periodontitis and atherosclerosis in response to polybacterial infection. *Pathog. Dis.* **2018**, *76*. [[CrossRef](#)]
49. Huck, O.; Elkaim, R.; Davideau, J.-L.; Tenenbaum, H. *Porphyromonas gingivalis* and its lipopolysaccharide differentially regulate the expression of cathepsin B in endothelial cells. *Mol. Oral Microbiol.* **2012**. [[CrossRef](#)]
50. Madan, M.; Amar, S. Toll-like receptor-2 mediates diet and/or pathogen associated atherosclerosis: Proteomic findings. *PLoS ONE* **2008**, *3*, e3204. [[CrossRef](#)]
51. Amar, S.; Wu, S.; Madan, M. Is *Porphyromonas gingivalis* cell invasion required for atherogenesis? Pharmacotherapeutic implications. *J. Immunol.* **2009**, *182*, 1584–1592. [[CrossRef](#)] [[PubMed](#)]
52. Cui, D.; Li, H.; Lei, L.; Chen, C.; Yan, F. Nonsurgical periodontal treatment reduced aortic inflammation in ApoE^{-/-} mice with periodontitis. *SpringerPlus* **2016**, *5*, 940. [[CrossRef](#)] [[PubMed](#)]

53. Akhi, R.; Wang, C.; Nissinen, A.E.; Kankaanpää, J.; Bloigu, R.; Paju, S.; Mäntylä, P.; Buhlin, K.; Sinisalo, J.; Pussinen, P.J.; et al. Salivary IgA to MAA-LDL and Oral Pathogens Are Linked to Coronary Disease. *J. Dent. Res.* **2019**, *98*, 296–303. [[CrossRef](#)] [[PubMed](#)]
54. Kyrklund, M.; Kumm, O.; Kankaanpää, J.; Akhi, R.; Nissinen, A.; Turunen, S.P.; Pussinen, P.; Wang, C.; Hörkö, S. Immunization with gingipain A hemagglutinin domain of *Porphyromonas gingivalis* induces IgM antibodies binding to malondialdehyde-acetaldehyde modified low-density lipoprotein. *PLoS ONE* **2018**, *13*, e0191216. [[CrossRef](#)]
55. Bugueno, I.M.; Khelif, Y.; Seelam, N.; Morand, D.-N.; Tenenbaum, H.; Davideau, J.-L.; Huck, O. *Porphyromonas gingivalis* Differentially Modulates Cell Death Profile in Ox-LDL and TNF- α Pre-Treated Endothelial Cells. *PLoS ONE* **2016**, *11*, e0154590-18. [[CrossRef](#)]
56. O'Connor, C.M.; Dunne, M.W.; Pfeffer, M.A.; Muhlestein, J.B.; Yao, L.; Gupta, S.; Benner, R.J.; Fisher, M.R.; Cook, T.D. Investigators in the WIZARD Study. Azithromycin for the Secondary Prevention of Coronary Heart Disease Events: The WIZARD Study: A Randomized Controlled Trial. *JAMA* **2003**, *290*, 1459–1466. [[CrossRef](#)]
57. Grayston, J.T.; Kronmal, R.A.; Jackson, L.A.; Parisi, A.F.; Muhlestein, J.B.; Cohen, J.D.; Rogers, W.J.; Crouse, J.R.; Borrowdale, S.L.; Schron, E.; et al. ACES Investigators. Azithromycin for the Secondary Prevention of Coronary Events. *N. Engl. J. Med.* **2005**, *352*, 1637–1645. [[CrossRef](#)]
58. Cannon, C.P.; Braunwald, E.; McCabe, C.H.; Grayston, J.T.; Muhlestein, B.; Giugliano, R.P.; Cairns, R.; Skene, A.M. Antibiotic treatment of Chlamydia pneumoniae after acute coronary syndrome. *N. Engl. J. Med.* **2005**, *352*, 1646–1654. [[CrossRef](#)]
59. Jespersen, C.M.; Als-Nielsen, B.; Damgaard, M.; Hansen, J.F.; Hansen, S.; Helø, O.H.; Hildebrandt, P.; Hilden, J.; Jensen, G.B.; Kastrup, J.; et al. Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. *BMJ* **2006**, *332*, 22–27. [[CrossRef](#)]
60. Joensen, J.B.; Juul, S.; Henneberg, E.; Thomsen, G.; Ostergaard, L.; Lindholt, J.S. Can long-term antibiotic treatment prevent progression of peripheral arterial occlusive disease? A large, randomized, double-blinded, placebo-controlled trial. *Atherosclerosis* **2008**, *196*, 937–942. [[CrossRef](#)]
61. Campbell, L.A.; Rosenfeld, M.E. Infection and Atherosclerosis Development. *Arch. Med. Res.* **2015**, *46*, 339–350. [[CrossRef](#)]
62. Grassi, W.; Angelis, R.D.; Lamanna, G.; Cervini, C. The clinical features of rheumatoid arthritis. *Eur. J. Radiol.* **1998**, *7*, S18–S24. [[CrossRef](#)]
63. Mantle, A. The Etiology of Rheumatism Considered from a Bacterial Point of View. *Br. Med. J.* **1887**, *1*, 1381–1384. [[CrossRef](#)]
64. Li, S.; Yu, Y.; Yue, Y.; Zhang, Z.; Su, K. Microbial Infection and Rheumatoid Arthritis. *J. Clin. Cell. Immunol.* **2013**, *4*. [[CrossRef](#)]
65. Bingham, C.O., 3rd; Moni, M. Periodontal disease and rheumatoid arthritis: The evidence accumulates for complex pathobiologic interactions. *Curr. Opin. Rheumatol.* **2013**, *25*, 345–353. [[CrossRef](#)]
66. Rutger, G.P. Rheumatoid arthritis and periodontitis—Inflammatory and infectious connections. Review of the literature. *J. Oral Microbiol.* **2012**, *4*. [[CrossRef](#)]
67. Chukkappalli, S.; Rivera-Kweh, M.; Gehlot, P.; Velsko, I.; Bhattacharyya, I.; Calise, S.J.; Satoh, M.; Chan, E.K.L.; Holoshitz, J.; Kesavalu, L. Periodontal bacterial colonization in synovial tissues exacerbates collagen-induced arthritis in B10.RIII mice. *Arthritis Res. Ther.* **2016**, *18*, 161. [[CrossRef](#)]
68. Okumura, G.; Kondo, N.; Sato, K.; Yamazaki, K.; Ohshima, H.; Kawashima, H.; Ogoe, A.; Endo, N. Experimental arthritis and *Porphyromonas gingivalis* administration synergistically decrease bone regeneration in femoral cortical defects. *Sci. Rep.* **2019**, *9*, 1–12. [[CrossRef](#)]
69. Huck, O.; You, J.; Han, X.; Cai, B.; Panek, J.; Amar, S. Reduction of Articular and Systemic Inflammation by Kava-241 in *Porphyromonas gingivalis*-induced Arthritis Murine Model. *Infect. Immun.* **2018**, *86*. [[CrossRef](#)]
70. Sugawara, M.; Yamashita, K.; Yoshie, H.; Hara, K. Detection of, and anti-collagen antibody produced by, CD5-positive B cells in inflamed gingival tissues. *J. Periodontal Res.* **1992**, *27*, 489–498. [[CrossRef](#)]
71. Harre, U.; Georgess, D.; Bang, H.; Bozec, A.; Axmann, R.; Ossipova, E.; Jakobsson, P.-J.; Baum, W.; Nimmerjahn, F.; Szarka, E.; et al. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. *J. Clin. Investig.* **2012**, *122*, 1791–1802. [[CrossRef](#)]

72. Elkaim, R.; Bugueno-Valdebenito, I.M.; Benkirane-Jessel, N.; Tenenbaum, H. *Porphyromonas gingivalis* and its LPS differentially regulate the expression of peptidyl arginine deiminases in human chondrocytes. *Innate Immun.* **2017**, *23*, 468–475. [[CrossRef](#)]
73. Maresz, K.J.; Hellvard, A.; Sroka, A.; Adamowicz, K.; Bielecka, E.; Koziel, J.; Gawron, K.; Mizgalska, D.; Marcinska, K.A.; Benedyk, M.; et al. *Porphyromonas gingivalis* facilitates the development and progression of destructive arthritis through its unique bacterial peptidylarginine deiminase (PAD). *PLoS Pathog.* **2013**, *9*, e1003627. [[CrossRef](#)]
74. Larsen, D.N.; Mikkelsen, C.E.; Kierkegaard, M.; Bereta, G.P.; Nowakowska, Z.; Kaczmarek, J.Z.; Potempa, J.; Højrup, P. Citrullinome of *Porphyromonas gingivalis* Outer Membrane Vesicles: Confident Identification of Citrullinated Peptides. *Mol. Cell. Proteom.* **2020**, *19*, 167–180. [[CrossRef](#)]
75. Casiano-Colón, A.; Marquis, R.E. Role of the arginine deiminase system in protecting oral bacteria and an enzymatic basis for acid tolerance. *Appl. Environ. Microbiol.* **1988**, *54*, 1318–1324. [[CrossRef](#)]
76. Niederman, R.; Brunkhorst, B.; Smith, S.; Weinreb, R.N.; Ryder, M.I. Ammonia as a potential mediator of adult human periodontal infection: Inhibition of neutrophil function. *Arch. Oral Biol.* **1990**, *35*, S205–S209. [[CrossRef](#)]
77. Dahlen, G.; Basic, A.; Bylund, J. Importance of Virulence Factors for the Persistence of Oral Bacteria in the Inflamed Gingival Crevice and in the Pathogenesis of Periodontal Disease. *J. Clin. Med.* **2019**, *8*, 1339. [[CrossRef](#)]
78. Jung, H.; Jung, S.M.; Rim, Y.A.; Park, N.; Nam, Y.; Lee, J.; Park, S.-H.; Ju, J.H. Arthritic role of *Porphyromonas gingivalis* in collagen-induced arthritis mice. *PLoS ONE* **2017**, *12*, e0188698. [[CrossRef](#)]
79. Peng, H.-Y.; Chen, S.-Y.; Siao, S.-H.; Chang, J.T.; Xue, T.-Y.; Lee, Y.-H.; Jan, M.-S.; Tsay, G.J.; Zouali, M. Targeting a cysteine protease from a pathobiont alleviates experimental arthritis. *Arthritis Res. Ther.* **2020**, *22*, 114. [[CrossRef](#)]
80. Kharlamova, N.; Jiang, X.; Sherina, N.; Potempa, B.; Israelsson, L.; Quirke, A.M.; Eriksson, K.; Yucel-Lindberg, T.; Venables, P.J.; Potempa, J.; et al. Antibodies to *Porphyromonas gingivalis* Indicate Interaction between Oral Infection, Smoking, and Risk Genes in Rheumatoid Arthritis Etiology. *Arthritis Rheumatol.* **2016**, *68*, 604–613. [[CrossRef](#)]
81. Carmona, L.; Cross, M.; Williams, B.; Lassere, M.; March, L. Rheumatoid arthritis. *Best Pract. Res. Clin. Rheumatol.* **2010**, *24*, 733–745. [[CrossRef](#)] [[PubMed](#)]
82. Kononoff, A.; Elfving, P.; Pussinen, P.; Hörkkö, S.; Kautiainen, H.; Arstila, L.; Laasonen, L.; Savolainen, E.; Niinisalo, H.; Rutanen, J.; et al. Association of rheumatoid arthritis disease activity and antibodies to periodontal bacteria with serum lipoprotein profile in drug naive patients. *Ann. Med.* **2020**, *52*, 32–42. [[CrossRef](#)]
83. de Molon, R.S.; Rossa, C., Jr.; Thurlings, R.M.; Cirelli, J.A.; Koenders, M.I. Linkage of Periodontitis and Rheumatoid Arthritis: Current Evidence and Potential Biological Interactions. *Int. J. Mol. Sci.* **2019**, *20*, 4541. [[CrossRef](#)] [[PubMed](#)]
84. Białoś, K.; Radwan-Oczko, M.; Duś-Ilnicka, I.; Korman, L.; Świerkot, J. Periodontal disease and influence of periodontal treatment on disease activity in patients with rheumatoid arthritis and spondyloarthritis. *Rheumatol. Int.* **2020**, *40*, 455–463. [[CrossRef](#)] [[PubMed](#)]
85. Keller, A.; Rohde, J.F.; Raymond, K.; Heitmann, B.L. The Association between Periodontal Disease and Overweight and Obesity: A Systematic Review. *J. Periodontol.* **2015**, 1–15. [[CrossRef](#)] [[PubMed](#)]
86. Le Sage, F.; Meilhac, O.; Gonthier, M.-P. *Porphyromonas gingivalis* lipopolysaccharide induces pro-inflammatory adipokine secretion and oxidative stress by regulating Toll-like receptor-mediated signaling pathways and redox enzymes in adipocytes. *Mol. Cell. Endocrinol.* **2017**, *446*, 102–110. [[CrossRef](#)]
87. Cani, P.D.; Amar, J.; Iglesias, M.A.; Poggi, M.; Knauf, C.; Bastelica, D.; Neyrinck, A.M.; Fava, F.; Tuohy, K.M.; Chabo, C.; et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **2007**, *56*, 1761–1772. [[CrossRef](#)]
88. Richard, G.; Trivedi, N.; Belta, C.; Amar, S. Partial restoration of macrophage alteration from diet-induced obesity in response to *Porphyromonas gingivalis* infection. *PLoS ONE* **2013**, *8*, e70320. [[CrossRef](#)]
89. Cani, P.D. Human gut microbiome: Hopes, threats and promises. *Gut* **2018**, *67*, 1716–1725. [[CrossRef](#)]

90. Tilg, H.; Moschen, A.R. Microbiota and diabetes: An evolving relationship. *Gut* **2014**, *63*, 1513–1521. [[CrossRef](#)] [[PubMed](#)]
91. Li, J.; Lin, S.; Vanhoutte, P.M.; Woo, C.W.; Xu, A. Akkermansia Muciniphila Protects against Atherosclerosis by Preventing Metabolic Endotoxemia-Induced Inflammation in Apoe^{-/-} Mice. *Circulation* **2016**, *133*, 2434–2446. [[CrossRef](#)]
92. Baquero, F.; Nombela, C. The microbiome as a human organ. *Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis.* **2012**, *18*, 2–4. [[CrossRef](#)]
93. Kundu, P.; Blacher, E.; Elinav, E.; Pettersson, S. Our Gut Microbiome: The Evolving Inner. *Self. Cell* **2017**, *171*, 1481–1493. [[CrossRef](#)] [[PubMed](#)]
94. Turnbaugh, P.J.; Ley, R.E.; Mahowald, M.A.; Magrini, V.; Mardis, E.R.; Gordon, J.I. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **2006**, *444*, 1027–1031. [[CrossRef](#)] [[PubMed](#)]
95. Pedersen, A.M.L.; Sørensen, C.E.; Proctor, G.B.; Carpenter, G.H.; Ekström, J. Salivary secretion in health and disease. *J. Oral Rehabil.* **2018**, *45*, 730–746. [[CrossRef](#)] [[PubMed](#)]
96. Saygun, I.; Nizam, N.; Keskiner, I.; Bal, V.; Kubar, A.; Açikel, C.; Serdar, M.; Slots, J. Salivary infectious agents and periodontal disease status. *J. Periodontal Res.* **2011**, *46*, 235–239. [[CrossRef](#)] [[PubMed](#)]
97. Arimatsu, K.; Yamada, H.; Miyazawa, H.; Minagawa, T.; Nakajima, M.; Ryder, M.I.; Gotoh, K.; Motooka, D.; Nakamura, S.; Iida, T.; et al. Oral pathobiont induces systemic inflammation and metabolic changes associated with alteration of gut microbiota. *Sci. Rep.* **2014**, *4*, 4828. [[CrossRef](#)]
98. Lourenço, T.G.B.; Spencer, S.J.; Alm, E.J.; Colombo, A.P. Defining the gut microbiota in individuals with periodontal diseases: An exploratory study. *J. Oral Microbiol.* **2018**, *10*, 1487741. [[CrossRef](#)]
99. Kato, T.; Yamazaki, K.; Nakajima, M.; Date, Y.; Kikuchi, J.; Hase, K.; Ohno, H.; Yamazaki, K.; D’Orazio, S.E.F. Oral Administration of *Porphyromonas gingivalis* Alters the Gut Microbiome and Serum Metabolome. *mSphere* **2018**, *3*, e00460-18. [[CrossRef](#)]
100. Nakajima, M.; Arimatsu, K.; Kato, T.; Matsuda, Y.; Minagawa, T.; Takahashi, N.; Ohno, H.; Yamazaki, K. Oral Administration of *P. gingivalis* Induces Dysbiosis of Gut Microbiota and Impaired Barrier Function Leading to Dissemination of Enterobacteria to the Liver. *PLoS ONE* **2015**, *10*, e0134234. [[CrossRef](#)]
101. Matsuda, Y.; Kato, T.; Takahashi, N.; Nakajima, M.; Arimatsu, K.; Minagawa, T.; Sato, K.; Ohno, H.; Yamazaki, K. Ligature-induced periodontitis in mice induces elevated levels of circulating interleukin-6 but shows only weak effects on adipose and liver tissues. *J. Periodontal. Res.* **2016**, *51*, 639–646. [[CrossRef](#)] [[PubMed](#)]
102. Nguyen, T.L.; Vieira-Silva, S.; Liston, A.; Raes, J. How informative is the mouse for human gut microbiota research? *Dis. Model. Mech.* **2015**, *8*, 1–16. [[CrossRef](#)] [[PubMed](#)]
103. Segata, N.; Haake, S.K.; Mannon, P.; Lemon, K.P.; Waldron, L.; Gevers, D.; Huttenhower, C.; Izard, J. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. *Genome Biol.* **2012**, *13*, R42. [[CrossRef](#)] [[PubMed](#)]
104. Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z. The metabolic syndrome. *Lancet* **2005**, *365*, 1415–1428. [[CrossRef](#)]
105. Cani, P.D.; Osto, M.; Geurts, L.; Everard, A. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. *Gut Microbes* **2012**, *3*, 279–288. [[CrossRef](#)]
106. Cani, P.D.; Bibiloni, R.; Knauf, C.; Waget, A.; Neyrinck, A.M.; Delzenne, N.M.; Burcelin, R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* **2008**, *57*, 1470–1481. [[CrossRef](#)]
107. Amar, S.; Zhou, Q.; Shaik-Dasthagirisaheb, Y.; Leeman, S. Diet-induced obesity in mice causes changes in immune responses and bone loss manifested by bacterial challenge. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 20466–20471. [[CrossRef](#)]
108. Zhou, Q.; Leeman, S.E.; Amar, S. Signaling mechanisms in the restoration of impaired immune function due to diet-induced obesity. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 2867–2872. [[CrossRef](#)]
109. Zhou, Q.; Leeman, S.E.; Amar, S. Signaling mechanisms involved in altered function of macrophages from diet-induced obese mice affect immune responses. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 10740–10745. [[CrossRef](#)]

110. Blasco-Baque, V.; Garidou, L.; Pomié, C.; Escoula, Q.; Loubieres, P.; Le Gall-David, S.; Lemaitre, M.; Nicolas, S.; Klopp, P.; Waget, A.; et al. Periodontitis induced by *Porphyromonas gingivalis* drives periodontal microbiota dysbiosis and insulin resistance via an impaired adaptive immune response. *Gut* **2017**, *66*, 872–885. [[CrossRef](#)]
111. Grossi, S.G.; Skrepncinski, F.B.; DeCaro, T.; Robertson, D.C.; Ho, A.W.; Dunford, R.G.; Genco, R.J. Treatment of Periodontal Disease in Diabetics Reduces Glycated Hemoglobin. *J. Periodontol.* **1997**, *68*, 713–719. [[CrossRef](#)] [[PubMed](#)]
112. Kiran, M.; Arpak, N.; Ünsal, E.; Erdoğan, M.F. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. *J. Clin. Periodontol.* **2005**, *32*, 266–272. [[CrossRef](#)] [[PubMed](#)]
113. Altay, U.; Gürgan, C.A.; Ağbaht, K. Changes in Inflammatory and Metabolic Parameters after Periodontal Treatment in Patients with and without Obesity. *J. Periodontol.* **2013**, *84*, 13–23. [[CrossRef](#)] [[PubMed](#)]
114. Lang, N.P.; Salvi, G.E.; Sculean, A. Nonsurgical therapy for teeth and implants—When and why? *Periodontology* **2019**, *79*, 15–21. [[CrossRef](#)] [[PubMed](#)]
115. Almeida, M.L.; Duarte, P.M.; Figueira, E.A.; Lemos, J.C.; Nobre, C.M.G.; Miranda, T.S.; de Vasconcelos Gurgel, B.C. Effects of a full-mouth disinfection protocol on the treatment of type-2 diabetic and non-diabetic subjects with mild-to-moderate periodontitis: One-year clinical outcomes. *Clin. Oral Investig.* **2019**. [[CrossRef](#)]
116. Harmouche, L.; Courval, A.; Mathieu, A.; Petit, C.; Huck, O.; Séverac, F.; Davideau, J.-L. Impact of tooth-related factors on photodynamic therapy effectiveness during active periodontal therapy: A 6-months split-mouth randomized clinical trial. *Photodiagnosis Photodyn. Ther.* **2019**, *27*, 167–172. [[CrossRef](#)]
117. Mombelli, A.; Almaghlouth, A.; Cionca, N.; Courvoisier, D.S.; Giannopoulou, C. Differential benefits of amoxicillin-metronidazole in different phases of periodontal therapy in a randomized controlled crossover clinical trial. *J. Periodontol.* **2015**, *86*, 367–375. [[CrossRef](#)]
118. Leininger, M.; Tenenbaum, H.; Davideau, J.-L. Modified periodontal risk assessment score: Long-term predictive value of treatment outcomes. *Retrospect. Study* **2010**, *37*, 427–435. [[CrossRef](#)]
119. Petit, C.; Schmeltz, S.; Burgy, A.; Tenenbaum, H.; Huck, O.; Davideau, J.-L. Risk factors associated with long-term outcomes after active and supporting periodontal treatments: Impact of various compliance definitions on tooth loss. *Clin. Oral Investig.* **2019**, *62*, 218–219. [[CrossRef](#)]
120. Huck, O.; Mulhall, H.; Rubin, G.; Kizelnik, Z.; Iyer, R.; Perpich, J.D.; Haque, N.; Cani, P.D.; de Vos, W.M.; Amar, S. *Akkermansia muciniphila* reduces *Porphyromonas gingivalis*-induced inflammation and periodontal bone destruction. *J. Clin. Periodontol.* **2019**. [[CrossRef](#)]
121. Martin-Cabezas, R.; Davideau, J.-L.; Tenenbaum, H.; Huck, O. Clinical efficacy of probiotic as an adjunctive therapy to non-surgical periodontal treatment of chronic periodontitis: A systematic review and meta-analysis. *J. Clin. Periodontol.* **2016**, *43*. [[CrossRef](#)] [[PubMed](#)]
122. Geraldo, B.M.C.; Batalha, M.N.; Milhan, N.V.M.; Rossoni, R.D.; Scorzoni, L.; Anbinder, A.L. Heat-killed *Lactobacillus reuteri* and cell-free culture supernatant have similar effects to viable probiotics during interaction with *Porphyromonas gingivalis*. *J. Periodontol. Res.* **2019**. [[CrossRef](#)] [[PubMed](#)]
123. Sun, M.; Liu, Y.; Song, Y.; Gao, Y.; Zhao, F.; Luo, Y.; Qian, F.; Mu, G.; Tuo, Y. The ameliorative effect of *Lactobacillus plantarum*-12 on DSS-induced murine colitis. *Food Funct.* **2020**. [[CrossRef](#)] [[PubMed](#)]
124. Everard, A.; Belzer, C.; Geurts, L.; Ouwerkerk, J.P.; Druart, C.; Bindels, L.B.; Guiot, Y.; Derrien, M.; Muccioli, G.G.; Delzenne, N.M.; et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 9066–9071. [[CrossRef](#)] [[PubMed](#)]
125. Plovier, H.; Everard, A.; Druart, C.; Depommier, C.; Van Hul, M.; Geurts, L.; Chilloux, J.; Ottman, N.; Duparc, T.; Lichtenstein, L.; et al. A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat. Med.* **2017**, *23*, 107–113. [[CrossRef](#)]
126. Everard, A.; Plovier, H.; Rastelli, M.; Van Hul, M.; de Wouters d’Oplinter, A.; Geurts, L.; Druart, C.; Robine, S.; Delzenne, N.M.; Muccioli, G.G.; et al. Intestinal epithelial N-acylphosphatidylethanolamine phospholipase D links dietary fat to metabolic adaptations in obesity and steatosis. *Nat. Commun.* **2019**, *10*, 457. [[CrossRef](#)]
127. Zhai, R.; Xue, X.; Zhang, L.; Yang, X.; Zhao, L.; Zhang, C. Strain-Specific Anti-inflammatory Properties of Two *Akkermansia muciniphila* Strains on Chronic Colitis in Mice. *Front. Cell. Infect. Microbiol.* **2019**, *9*, 239. [[CrossRef](#)]

128. Cani, P.D.; de Vos, W.M. Next-Generation Beneficial Microbes: The Case of *Akkermansia muciniphila*. *Front. Microbiol.* **2017**, *8*, 1765. [[CrossRef](#)]
129. Ottman, N.; Reunanen, J.; Meijerink, M.; Pietilä, T.E.; Kainulainen, V.; Klievink, J.; Huuskonen, L.; Aalvink, S.; Skurnik, M.; Boeren, S.; et al. Pili-like proteins of *Akkermansia muciniphila* modulate host immune responses and gut barrier function. *PLoS ONE* **2017**, *12*, e0173004. [[CrossRef](#)]
130. Depommier, C.; Everard, A.; Druart, C.; Plovier, H.; Van Hul, M.; Vieira-Silva, S.; Falony, G.; Raes, J.; Maiter, D.; Delzenne, N.M.; et al. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: A proof-of-concept exploratory study. *Nat. Med.* **2019**, *25*, 1096–1103. [[CrossRef](#)]



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).