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Review

Periodontal and Systemic Diseases: Shared Pathophysiology

Neda Najafimakhsoos [1] and Claudio Cesari [2*]

[1] Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Via San Vitale 59, 40125 Bologna, Italy

[2] Periodontal Unit, Department of Dentistry, Vita-Salute San Raffaele University, Universtiy of Milan, Via Olgettina 58, 20132 Milan, Italy

[*] Correspondence: c.cesari1@docenti.unisr.it

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Abstract: Periodontitis is a chronic, progressive inflammatory disease characterized by the gradual destruction of the supporting structures of the teeth, including the periodontal ligament and alveolar bone. This condition primarily originates from microbial dysbiosis in the oral cavity, further influenced by the host's immune responses and a variety of environmental and behavioral factors. As the leading cause of tooth loss and edentulism among adults, periodontitis also has far-reaching systemic consequences. An expanding body of scientific evidence has established strong associations between periodontitis and numerous systemic conditions, including cardiovascular disease, diabetes mellitus, respiratory disorders, thyroid dysfunction, and obstructive sleep apnea (OSA). This review examines the potential biological and clinical connections between periodontitis and these systemic diseases by first providing an overview of the normal physiological functions and pathological changes of each condition. It then explores the shared immunological and pathophysiological pathways, with particular focus on inflammatory mediators, immune system dysregulation, and microbial translocation. By integrating perspectives from disciplines such as microbiology, immunology, and clinical research, this review underscores the integral role of oral health in systemic well-being. It also highlights the necessity of early detection, interdisciplinary cooperation, and preventive strategies—including lifestyle modifications—to manage common risk factors and improve comprehensive patient outcomes.

Keywords: Periodontal Disease; Systemic Disease; Cardiovascular Disease; Diabetes; Respiratory Disease; Thyroid Disease; OSA; Sleep Apnea

1. Periodontal Disease

An equilibrium in the oral microbial community is essential for internal balance, with commensal bacteria serving as a natural defense against external and harmful microbes [1–3]. The oral microbiota comprises over 700 species, which are rarely found in a free-floating state [1–3]. Instead, they form well-structured biofilms [3]. Biofilms are organized communities of bacteria embedded in an extracellular matrix, which enables them to adhere firmly to tooth surfaces and resist mechanical removal [4].This matrix creates an optimal environment for bacterial proliferation, genetic exchange, and increased resistance to antimicrobial agents [4]. The extracellular matrix also provides essential nutrients that support microbial growth and help maintain biofilm stability [3]. It facilitates the attachment of biofilms to oral tissues and protects microorganisms from immune responses and antimicrobial treatments [3,5] Within biofilms, bacteria communicate through quorum sensing—a process by which they release

signaling molecules to coordinate biofilm development, enhance growth, regulate virulence factor expression, and promote disease progression [3].

In a non-pathological oral cavity, the predominant bacteria include *Streptococcus*, *Prevotella*, *Haemophilus*, *Fusobacterium*, and *Veillonella* [3,6]. These microorganisms do not induce inflammation and contribute to oral health by producing substances that compete with and inhibit the colonization of pathogenic bacteria [3,7]. When more than two species rely on the same nutrient source, some may be suppressed while others outcompete and exclude them [8]. A stable microbial balance is achieved when multiple species with mutualistic relationships coexist over time [8]. Environmental changes can shift competitive advantages, leading to fluctuations in species dominance within the community [8]. New species may occasionally enter the ecosystem, while others diminish or disappear. Interactions like synergism—where one species provides nutrients beneficial to another—and antagonism—where one produces substances harmful to others—play crucial roles in maintaining this ecological equilibrium [8]. Microbial diversity in subgingival plaque increases as the oral environment shifts from health to disease, such as gingivitis and periodontitis. This rise is due to the greater quantity and variety of nutrients from exudate produced during gingival inflammation, creating conditions favorable for a broader range of microbial species [9].

Tobacco smoking affects the incidence and progression of periodontitis by altering the composition of the subgingival biofilm, delaying neutrophil recruitment and migration to periodontal tissues, and compromising the acute immune response [10,11]. It increases the threshold of microbial accumulation needed to trigger the inflammatory cascade in periodontal tissues [11]. Smoking also shifts neutrophil activity toward a more destructive profile by elevating interleukin-1 and interleukin-6, upregulating bone resorption, and increasing the RANKL/osteoprotegerin (OPG) ratio [11]. Additionally, it leads to higher concentrations of elastase and matrix metalloproteinases (MMP-8 and MMP-9), while reducing the levels of protease inhibitors such as alpha-2-macroglobulin and alpha-1-antitrypsin [10,11]. This results in enhanced collagen degradation combined with reduced vascularization of gingival tissues, ultimately impairing periodontal healing [10,11].

Local irritants, such as rough surfaces on dental restorations, can also promote inflammation by creating irregular areas that facilitate microbial colonization and the maturation of oral plaque [1].

Periodontal disease is a complex, multifactorial inflammatory condition that affects the supporting structures of the teeth, leading to progressive tissue destruction and, in severe cases, tooth loss [4]. It typically begins as gingivitis—a mild and reversible inflammation of the gingiva caused by the accumulation of dental plaque. If left untreated, gingivitis can progress to periodontitis, a more advanced form marked by the destruction of periodontal ligament fibers, alveolar bone loss, and the formation of periodontal pockets [4].

The primary bacteria responsible for periodontal disease are anaerobic Gram-negative organisms, collectively known as the red complex. This group includes *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* [4].

Porphyromonas gingivalis contributes to periodontitis by disrupting immune homeostasis and promoting oral microbial dysbiosis [12–14]. Despite its low abundance, it functions as a keystone pathogen through a range of virulence factors, including lipopolysaccharide (LPS), gingipains, fimbriae, and a polysaccharide capsule [14]. The LPS, depending on its acylation pattern, can activate or inhibit Toll-like receptors (TLR2 or TLR4), leading either to inflammation via NF-κB and MAPK pathways or to immune evasion through TLR4 and caspase-11 inhibition [12–14]. Gingipains, potent proteases, degrade extracellular matrix proteins, cytokines, and complement components (C3, C5), thereby impairing opsonization, inhibiting membrane attack complex (MAC) formation, and amplifying C5a-driven inflammation. Fimbriae facilitate adhesion to host cells and coaggregation with other microbes, and exploit receptors such as CR3 and CXCR4 to block IL-12 production and evade immune clearance. Short fimbriae (Mfa1) interfere with dendritic cell autophagy, supporting intracellular survival [14]. The capsule shields the bacterium from phagocytosis, modulates cytokine responses, and promotes persistence and microbial coaggregation. *P. gingivalis* also alters T cell dynamics, enhancing Th17 or Th2 polarization, inhibiting T cell proliferation via receptor cleavage, and reprogramming regulatory T cells (Tregs) into IL-17–producing cells, thus sustaining chronic inflammation and alveolar bone loss [14].

Tannerella forsythia exacerbates inflammation by producing proteases and evading host immune defenses. Its cell wall lipopolysaccharide (LPS) activates immune cells, triggering the release of proinflammatory cytokines such as TNF-α, IL-1, and IL-6 [3,15].

Aggregatibacter actinomycetemcomitans is frequently found in the advanced stages of periodontitis and cases

of localized aggressive periodontitis [3]. It produces leukotoxin A, which disrupts the antiinflammatory activity of leukocytes [3]. In response to *A. actinomycetemcomitans*, macrophages release proinflammatory cytokines such as IL-1 and TNF-α. Moreover, macrophages exhibit increased sensitivity to these cytokines, leading to caspase-1 activation and excessive secretion of IL-1β [3]. Following microbial invasion, the activation of tissue and immune cells leads to the release of proinflammatory mediators such as cytokines and chemokines. These molecules initiate a localized immune response through a positive feedback loop [3,16]. Cytokines promote the recruitment of immune cells to the infection site, while simultaneously impairing extracellular matrix synthesis and compromising gingival soft tissue homeostasis. This inflammatory cascade disrupts the balance between osteoblast and osteoclast activity, favoring osteoclastogenesis and resulting in alveolar bone resorption [3,16].

Inflammation plays a central role in periodontal tissue destruction. The host immune response to periodontal pathogens involves both the innate and adaptive immune systems. Neutrophils serve as the first line of defense, releasing reactive oxygen species and proteolytic enzymes to combat bacterial invasion. However, excessive neutrophil activity can cause collateral tissue damage, including degradation of the extracellular matrix and stimulation of bone resorption [4].

Macrophages and dendritic cells further amplify the inflammatory response by presenting bacterial antigens to T lymphocytes, thereby activating the Th1 and Th17 pathways [4]. Th1 cells release interferon-gamma, which enhances macrophage activity, while Th17 cells secrete interleukin-17, promoting neutrophil recruitment and osteoclast activation. These immune processes collectively contribute to alveolar bone loss and increased tooth mobility [4].

Beyond localized damage, periodontal disease can have systemic effects. One key mechanism is the dissemination of periodontal pathogens and inflammatory mediators—such as C-reactive protein and fibrinogen—into the bloodstream [4]. This may occur through bacteremia induced by chewing, brushing, or dental procedures, allowing oral microbes to reach distant organs and potentially impact systemic health [4].

2. Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) is marked by lipid accumulation and the development of atheromatous plaques within the arterial walls [17–19]. Similar to periodontitis, ASCVD is a chronic inflammatory condition with serious long-term consequences, including stroke, aortic aneurysm, and myocardial infarction [17].

Following an extensive review, the American Heart Association (AHA) reported a significant, independent association between periodontitis (PD) and arteriosclerotic vascular disease (ASVD), supported by level A evidence [20]. Multiple mechanisms have been proposed to explain this relationship. PD-driven systemic inflammation is reflected by elevated levels of biomarkers such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). Furthermore, the activation of toll-like receptors (TLRs) on endothelial and immune cells initiates NF-κB signaling pathways, which promote the expression of adhesion molecules, endothelial dysfunction, and increased production of proinflammatory cytokines [20]. Lipopolysaccharides (LPS) and heat-shock proteins from periodontal pathogens may also induce molecular mimicry, potentially triggering autoimmune responses via T and B lymphocytes. Additionally, direct vascular injury by periodontal bacteria entering the bloodstream has been suggested [20].

Importantly, gram-negative bacteria commonly implicated in PD—such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Treponema denticola*—can enter the bloodstream during routine oral activities [20]. Once systemic, their LPS components activate endothelial cells and contribute to vascular inflammation, engaging both innate and adaptive immune responses [20]. Although periodontal therapy has shown improvements in systemic inflammatory markers and surrogate measures of subclinical arterial disease, the AHA concluded that current evidence does not yet establish a causal link between PD treatment and reduced cardiovascular events [20].

In the pathogenesis of atherosclerosis, three key conditions are essential for the formation of atheromatous plaques [20]:

1. Elevated apolipoprotein B (ApoB), which strongly correlates with circulating levels of low-density lipoprotein (LDL).
2. Increased vascular permeability, allowing the entry of monocytes and lipopolysaccharides (LPS) into the intimal layer.

3. Adhesion of monocytes and lipoproteins to the vascular endothelium [20].

Periodontal disease is increasingly recognized as a systemic contributor to atherogenesis. Major periodontal pathogens—including *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, and *Tannerella forsythia*—have been implicated in all three of these pathogenic mechanisms.

These microorganisms initially secrete phospholipase A2, which facilitates the production of small dense LDL (sdLDL) particles, strongly associated with elevated ApoB—a well-established predictor of atherosclerotic cardiovascular disease (ASCVD) [20]. Moreover, their LPS compromises endothelial integrity by increasing vascular permeability. LPS engages toll-like receptors (TLRs) on endothelial cells, activating the NF-κB signaling pathway and stimulating the release of tumor necrosis factor-alpha (TNF-α), which disrupts tight junctions and further enhances endothelial permeability [21,22].

In addition, leukotoxin produced by *Aggregatibacter actinomycetemcomitans* induces apoptosis in endothelial cells, further contributing to increased vascular permeability [23]. These pathogenic effects collectively lead to the upregulation of adhesion molecules, enhanced monocyte infiltration into the vascular wall, and amplification of systemic inflammation through activation of the innate immune system [23].

A critical step in atherogenesis is the retention of lipoproteins within the intimal layer of blood vessels. Vascular smooth muscle cells (VSMCs) exhibit two phenotypes: the contractile phenotype, predominant in the medial layer of arteries, and the synthetic phenotype, which migrates to the intimal layer. The synthetic phenotype secretes elevated levels of proteoglycans—negatively charged molecules that bind strongly to the positively charged amino acids of apolipoprotein B (ApoB). This interaction facilitates the retention of lipoproteins in the intima, a fundamental event in atheromatous plaque development [20].

Notably, periodontal bacteria promote the phenotypic switch of VSMCs from a contractile to a synthetic state, thereby increasing proteoglycan production and enhancing lipoprotein binding in the vascular wall [20]. *P. gingivalis*, in particular, has been shown to upregulate the expression of angiopoietin-2 (Angpt2), which plays a key role in driving this phenotypic transformation [20].

A relevant clinical consideration is whether atherosclerosis linked to periodontitis can be distinguished from atherosclerosis driven by other risk factors. Although both pathways involve similar inflammatory mechanisms, molecular studies have demonstrated a unique microbial signature within atheromatous plaques. For instance, Gaetti-Jardim E Jr. et al. analyzed 44 patients undergoing coronary endarterectomy and found that 39 exhibited clinical signs of periodontal disease. Remarkably, 64% of the atheroma samples contained DNA from two or more periodontal pathogens, with *P. gingivalis* and *A. actinomycetemcomitans* being the most frequently identified [24]. Similarly, Figuero et al. analyzed 42 carotid endarterectomy specimens for oral bacterial DNA and reported that every atheroma sample contained at least one species of oral bacteria. Multiple pathogens were frequently identified, with *P. gingivalis* and *A. actinomycetemcomitans* being the most prevalent [25].

These findings suggest that the presence of specific oral pathogens within atheromatous plaques may represent a microbial signature, potentially distinguishing periodontitis-associated atherosclerosis from atherosclerosis driven by other etiologies.

Moreover, periodontal bacteria can translocate into the systemic circulation, releasing endotoxins such as lipopolysaccharides (LPS). These LPS molecules trigger the release of proinflammatory cytokines and are strongly associated with elevated systemic inflammatory markers, including C-reactive protein (CRP), interleukin-1, and fibrinogen. Such markers are linked to a higher incidence of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism [26].

Clinical studies have demonstrated that periodontal therapy—particularly with antibiotic regimens such as amoxicillin-metronidazole or tetracyclines—can significantly reduce systemic inflammatory markers, indicating a potential cardioprotective benefit [20,26].

Beyond the established correlation between periodontal pathogens and atherosclerosis, other Gram-positive bacteria residing in the oral cavity—such as *Streptococcus* and *Staphylococcus* species—can also trigger inflammation of the cardiac intima [27]. When these organisms enter the bloodstream, particularly during invasive dental procedures, they may contribute to the pathogenesis of infective endocarditis [27]. According to the American Heart Association, antibiotic prophylaxis is advised before dental procedures involving manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa in patients at elevated risk for infective endocarditis [27]. This high-risk group includes individuals with a history of infective endocarditis, prosthetic cardiac valves,

cardiac transplants complicated by valvular regurgitation, unrepaired cyanotic congenital heart diseases—such as Tetralogy of Fallot, truncus arteriosus, transposition of the great vessels, tricuspid atresia, and total anomalous pulmonary venous return—and those with repaired congenital heart defects accompanied by residual shunts or valvular regurgitation [27]. These recommendations are based on the risk of bacteremia and subsequent infective endocarditis, primarily involving oral *streptococci* and *staphylococci* [27].

These insights underscore the significant systemic impact of periodontal disease, affirming that it is not merely a localized oral pathology [28]. Identification and management of shared risk factors—such as tobacco use, physical inactivity, and socioeconomic disadvantage—are essential. Additional systemic contributors, including chronic stress, obesity, systemic lupus erythematosus (SLE), and multiple myeloma, may further aggravate endothelial dysfunction and systemic inflammation, both of which are central to the pathogenesis of hypertension [26,27].

Collaboration between cardiologists and periodontists is crucial for developing integrated treatment strategies, particularly since many patients remain unaware of the association between periodontitis and cardiovascular disease [28]. Clinicians should prioritize patient education, emphasizing the connection between oral and cardiovascular health and advocating for both preventive dental care and cardiovascular risk management [27,28]. Early identification of periodontitis in at-risk individuals may facilitate timely intervention and help prevent systemic complications. Emerging evidence also indicates that periodontal therapy can support blood pressure regulation and improve overall cardiovascular outcomes [28].

3. Diabetes

Diabetes mellitus is a metabolic disease characterized by high blood glucose levels, resulting from the body's inability to produce or respond properly to insulin [29]. It is commonly associated with the classic symptoms of polydipsia (excessive thirst), polyphagia (increased hunger), and polyuria (frequent urination). Diabetes is broadly classified into Type 1 and Type 2:

- Type 1 diabetes (5–10% of cases) has a juvenile onset and is insulin-dependent. It results from an autoimmune destruction of pancreatic beta cells, which produce insulin. This form is not preventable and requires lifelong insulin therapy. Common signs include fruity-smelling breath (ketone breath) and a rapid onset of symptoms [29].
- Type 2 diabetes (90%–95% of cases) typically has adult onset and is initially non-insulin-dependent [30]. It is mainly caused by insulin resistance and is often modifiable or preventable through dietary and lifestyle interventions. In advanced stages, insulin therapy may become necessary [29,31,32].

There is a well-established correlation between diabetes and periodontitis. Diabetes exacerbates periodontal inflammation, with hyperglycemia playing a key role by increasing the concentration of free radicals in plasma [33,34]. One major mechanism is non-enzymatic glycation, where advanced glycation end-products (AGEs) are formed. AGEs promote the generation of reactive oxygen species (ROS), such as superoxide (O_2-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH−) [33,34]. This oxidative stress is linked to pancreatic beta cell dysfunction, impairing insulin production [35,36]. Oxidative radicals also impair the proper formation and function of gap junctions in blood vessels [37,38]. AGEs bind to receptors on endothelial cells, macrophages, and neutrophils, leading to the activation of protein kinase C (PKC), a key signaling pathway in oxidative stress [39]. This activation results in increased production of free radicals and proinflammatory cytokines by monocytes and endothelial cells, contributing to chronic inflammation and progressive tissue destruction [39].

Diabetes suppresses the innate immune response by reducing both the number and chemotactic activity of neutrophils migrating from the bloodstream [38] and leads to a decrease in nerve growth factor (NGF), a neurotrophic factor. NGF, expressed by fibroblasts, endothelial cells, and keratinocytes, plays a crucial role in vascularization [37].

Additionally, AGEs disrupt collagen turnover by reducing collagen synthesis and increasing the activity of collagenases, particularly matrix metalloproteinases (MMP-1, MMP-8, and MMP-13). This enzymatic activity compromises the structural integrity of periodontal tissues [33,39]. Polymorphonuclear leukocytes (PMNLs), which serve as the first line of defense in the oral cavity, exhibit functional impairments in diabetes, negatively affecting the immune response and increasing susceptibility to periodontitis [33,39].

Moreover, hyperglycemia leads to non-enzymatic glycation of collagen, forming cross-links between collagen

molecules. This reduces collagen solubility and causes the accumulation of AGE-modified collagen in the periodontium of diabetic patients, impairing tissue healing after periodontal therapy [39,40].

Diabetes and chronic hyperglycemia also disturb the balance between the host and oral commensal microbiota, leading to dysbiosis [39]. Although scientific evidence on microbiota changes in poorly controlled diabetes is not entirely consistent, most studies suggest that inadequate glycemic control significantly impacts the periodontal microbiota, promoting dysbiosis [39]. Patients with poorly controlled diabetes exhibit a higher prevalence of red complex bacteria—*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*—in the subgingival biofilm. This increase correlates with elevated HbA1c levels [41].

Additionally, these patients show higher levels of RANKL and an increased RANKL/osteoprotegerin ratio. RANK is expressed on pre-osteoclasts and osteoblasts, while RANKL is a membrane-bound or secreted protein primarily produced by T cells [39,42].

This imbalance contributes to bone resorption. Hyperglycemia, via advanced glycation effects on leukocytes and periodontal ligament (PDL) fibroblasts, induces the expression of proinflammatory cytokines—including interleukins (IL-1, IL-6, IL-17, IL-23, IL-4, IL-12), tumor necrosis factor-alpha (TNF-α), M-CSF, MIP-1α, Substance P, C-reactive protein (CRP), inducible nitric oxide synthase (iNOS), resistin, and matrix metalloproteinases (MMPs)—which collectively promote periodontal tissue breakdown [39,42].

Furthermore, hyperglycemia promotes the upregulation of toll-like receptors (TLR-2 and TLR-4) on leukocytes and periodontal ligament (PDL) fibroblasts, enhancing their pattern recognition capabilities and amplifying the inflammatory response [39,43]. This contributes to microbial dysbiosis and periodontal destruction, as well as to enhanced osteoclast activation and bone resorption, which explains the increased irreversible loss of periodontal supporting structures, including alveolar bone, observed in diabetic patients [39,43].

Diabetes also impairs wound healing by reducing vascular circulation, leading to tissue hypoxia, an exaggerated initial inflammatory response, and increased production of oxidative free radicals [38]. Additionally, saliva from diabetic patients contains lower levels of glutathione and melatonin—both critical free radical scavengers [44,45]. The combination of reduced antioxidant defenses and elevated oxidative stress prolongs wound healing in diabetic individuals [37].

Periodontitis, in turn, influences diabetes progression by increasing oxidative stress markers such as C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-6 (IL-6), and fibrinogen [33,46]. Periodontal disease contributes to insulin resistance in type 2 diabetes patients by elevating proinflammatory mediators, including TNF-α, IL-1, IL-6, and prostaglandin E2 (PGE2) [7**?** –48]. Moreover, periodontal pathogens stimulate the production of proinflammatory cytokines and oxidative stress, further impairing insulin sensitivity and potentially contributing to the onset or worsening of diabetes mellitus [33,46].

DNA methylation, primarily mediated by DNA methyltransferases (DNMTs), plays a crucial role in gene regulation and maintaining epigenetic stability [48]. The methylation product, 5-methylcytosine (5mC), can be further oxidized to 5-hydroxymethylcytosine (5hmC) by the ten-eleven translocation (TET) protein family, particularly TET2 [49]. This oxidation represents a key step in active DNA demethylation.

Importantly, the conversion of 5mC to 5hmC depends not only on TET enzymes but also on the cofactor alpha-ketoglutarate (α-KG), which is synthesized by isocitrate dehydrogenases (IDHs) [50,51]. The presence of 5hmC facilitates DNA demethylation and is strongly linked to gene expression, especially in pathways involved in inflammation [51]. In periodontology, aberrant DNA methylation patterns affecting inflammatory genes have been documented, connecting these epigenetic changes to periodontal disease progression [52].

Genetic variations in the TET2 gene—specifically the AA and AC genotypes—have been associated with an increased susceptibility to periodontitis. Notably, the AA genotype correlates with elevated glycated hemoglobin (HbA1c) levels, suggesting an interplay between metabolic and inflammatory pathways [51, 53]. Beyond DNA demethylation, TET2 also oxidizes 5mC in RNA within innate immune cells, highlighting its broader role in regulating immune responses [54,55].

Furthermore, α-ketoglutarate (α-KG) and HbA1c levels exhibit a positive correlation, suggesting a metabolic-epigenetic feedback loop [50]. α-KG is essential in the TET2-mediated demethylation pathway, facilitating the enzymatic conversion of 5hmC back to cytosine [53]. In individuals with diabetes and HbA1c levels around 10%, significantly reduced 5hmC levels have been observed compared to healthy controls. This reduction is likely due to TET2 instability caused by hyperglycemia [51,56].

Collectively, these findings indicate that chronic hyperglycemia may impair TET2 function, disrupting normal DNA demethylation. This mechanistic link may underlie the epigenetic alterations seen in metabolic disorders like diabetes as well as inflammatory diseases such as periodontitis [51].

There is a well-established bidirectional relationship between periodontal disease and diabetes, with each condition exacerbating the severity of the other. Periodontal disease has also been identified as the sixth complication of diabetes due to the strong association between hyperglycemia and periodontal inflammation. Elevated blood glucose impairs immune function and promotes the formation of advanced glycation end products (AGEs), both of which contribute to periodontal tissue destruction [4].

4. Respiratory Disease

Chronic Obstructive Pulmonary Disease (COPD) is an irreversible condition with two main clinical manifestations: chronic bronchitis and emphysema [55,57].

- Emphysema is characterized by the permanent enlargement and destruction of airspaces distal to the terminal bronchioles. It commonly affects older, thin patients [55,57]. Clinical features include severe dyspnea, a "quiet" chest, hyperinflated lungs with flattened diaphragms, and enlarged alveoli. These patients are often called "pink puffers" because they maintain oxygenation despite labored breathing. Emphysema primarily affects the alveoli—the functional units of the lung—and is usually not associated with significant cough, mucus production, or wheezing [55,57].
- Chronic bronchitis is diagnosed when a patient has a daily productive cough for at least three months over two consecutive years. These patients tend to be overweight and cyanotic, with elevated hemoglobin levels, peripheral edema, wheezing, and rhonchi [55–57]. Chest X-rays may appear normal, but bronchial inflammation is present [55–57]. These patients are often referred to as "blue bloaters."

Asthma is a chronic inflammatory airway disease characterized by reversible episodes of airway hyper-responsiveness, dyspnea, chest tightness, coughing, and wheezing, leading to breathing difficulties [58].

The severity of periodontitis is higher in patients with lung diseases such as asthma and COPD. Periodontal bacteria residing in periodontal pockets can be aspirated into the lungs, where they contribute to airway epithelial apoptosis, increase adhesion of respiratory pathogens, promote mucin expression, and deregulate immune responses. This interplay plays a role in the initiation and progression of pulmonary diseases [59,60].

Patients without COPD exhibit a lower incidence of periodontitis compared to those with COPD [61]. Similarly, bleeding on probing (BOP), clinical attachment loss (CAL), and the incidence of periodontitis are significantly higher in patients with severe asthma [62]. Individuals with periodontitis have a 2–4-fold increased risk of developing asthma compared to those without periodontitis [62–64], possibly due to the long-term use of corticosteroids, which reduce mandibular bone mineral density and increase the risk of tooth loss [60,65]. Additionally, mouth breathing and consequent oral mucosal dehydration, along with elevated IgE levels in gingival tissues, may contribute to immune dysregulation [60,66].

Many bacteria involved in pulmonary infections are also commonly found in periodontitis. Red complex bacteria commonly associated with periodontitis—such as *Porphyromonas gingivalis*, *Treponema denticola*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, and *Tannerella forsythia*—are frequently linked to lung diseases, especially COPD [67,68]. Specifically, *F. nucleatum* and *A. actinomycetemcomitans* are prevalent in emphysema [69,70], while *P. intermedia* is often associated with asthma [71].

P. gingivalis and *Fusobacterium nucleatum*, commonly found in periodontal pockets, have been identified in the lungs of patients with pneumonia, suggesting that oral bacteria may serve as a reservoir for respiratory pathogens [4] .

Periodontal bacteria contribute to respiratory infections by altering receptor expression on epithelial mucosa, promoting pathogen aggregation, and enhancing invasion and adhesion of pathogens (e.g., in Hep-2 cells). This leads to caspase-3 activation and release of proinflammatory cytokines [62]. They can also induce apoptosis of pulmonary epithelial cells and disrupt the epithelial barrier by causing cell separation and loss of adherence [60,72].

The platelet-activating factor receptor (PAFr) is a key bacterial adhesion receptor on respiratory epithelial cells [60]. *Streptococcus pneumoniae* binds to PAFr, and certain periodontal bacteria increase *S. pneumoniae* adhesion to this receptor [60].

Periodontal bacteria, particularly *P. gingivalis*, can upregulate mucin expression. Patients with periodontitis may aspirate saliva containing these bacteria, potentially contributing to COPD development. Additionally, periodontal bacteria and neutrophils release chemokines and cytokines that regulate immune cells, causing an imbalance between Th17 and Treg cells—with elevated Th17 and decreased Treg levels [60, 73]. Th17 cells release cytokines such as IL-17, IL-23, IL-6, and GM-CSF, promoting pulmonary injury. A reduction in Treg cells results in increased IL-1β and IL-6, further worsening lung damage [60,74].

Finally, elevated systemic cytokines and chemokines induced by periodontal inflammation can indirectly promote the occurrence and progression of lung diseases [60].

Studies have shown that individuals with periodontitis exhibit an increased risk of COPD exacerbations, emphasizing the importance of oral health maintenance in pulmonary management. Additionally, the reduction of oral bacterial load through periodontal treatment has been associated with a decreased incidence of respiratory infections, further supporting the role of periodontal care in respiratory disease [4].

5. Thyroid Disease

The thyroid gland consists of follicular and parafollicular (C) cells. Follicular cells produce the thyroid hormones T3 (triiodothyronine) and T4 (thyroxine) [75–77], which regulate body temperature, metabolic rate, bone growth and remodeling, soft tissue healing, heart rate, and overall growth and maturation. Parafollicular cells secrete calcitonin, a hormone that helps lower serum calcium levels [75–77].

Thyroid disorders include hyperthyroidism and hypothyroidism.

- Hyperthyroidism is often caused by Graves' disease, an autoimmune condition in which autoantibodies target TSH receptors, stimulating excessive thyroid hormone production [78]. Symptoms include fatigue, nervousness, heat intolerance, weight loss, tachycardia, exophthalmos, and goiter, with elevated T3 and T4 levels. Bone remodeling changes in hyperthyroidism typically involve normal resorption depth but reduced osteon wall thickness [78].
- Hypothyroidism is commonly caused by iodine deficiency in underdeveloped countries and by Hashimoto's thyroiditis in developed countries. In Hashimoto's, antithyroglobulin antibodies attack thyroid tissue, leading to reduced levels of T3 and T4. Symptoms include weight gain, cold intolerance, bradycardia, and goiter. Bone remodeling in hypothyroidism is characterized by reduced resorption depth and increased osteon wall thickness [78].

Cretinism, a severe form of hypothyroidism in children, causes profound physical and mental developmental delays.

A potential link exists between periodontitis and thyroid disorders. Cytokines involved in periodontal inflammation—IL-1, IL-6, IL-10, IFN-γ, and TNF-α—are also present in thyroid follicular cells [78–82]. Dysbiosis of the oral microbiota in periodontitis may trigger autoimmune conditions like autoimmune thyroid diseases (AITD) [78–82]. Type 1 lymphocytes can stimulate thyroidal IFN-γ and TNF-α, promoting CXCL10 expression and perpetuating the autoimmune process, especially in hyperthyroidism [78–82].

Moreover, thyroid hormones increase oxidative stress by promoting reactive oxygen species (ROS) production and impairing antioxidant defenses. Disruption of these local antioxidant systems may contribute to systemic inflammatory responses [78–82].

Song et al. demonstrated that suppressed TSH levels are associated with a higher prevalence of periodontitis [83]. Bhankhar et al. reported a reduction in TSH levels in hypothyroid patients three months after non-surgical periodontal therapy, suggesting that such treatment can improve periodontal health by reducing inflammatory markers and potentially influencing thyroid function [78,84]. Similarly, Chen et al. found that individuals with periodontitis have an increased risk of thyroid cancer, and that periodontal treatment can reduce this risk [78,85]. Moreover, periodontal conditions tend to worsen in patients with hypothyroidism [78].

Literature has also reported that a high Community Periodontal Index (CPI) is associated with abnormalities in thyroid function tests [86,87]. A positive relationship has been found between hypothyroidism and periodontitis [86,88]. Furthermore, thyroid dysfunction is significantly linked to the development of periodontitis, independent of various known risk factors [86,89].

Periodontal bacteria can express GroEL-like proteins, members of the Hsp60 family. Elevated Hsp60 levels

have been found in both the blood and thyroid tissue of patients with hypothyroidism [86,90,91]. These proteins exhibit structural similarities with thyroglobulin and thyroid peroxidase, potentially contributing to autoimmune thyroid responses [86,90,91].

Observational studies indicate that patients with lower TSH levels and hypothyroidism have a higher risk of both bone fractures and periodontitis [83,92,93]. One study also demonstrated that elevated TSH levels can inhibit osteogenic differentiation of periodontal ligament stem cells *in vitro* [86,92].

Moreover, Gao et al., through Mendelian Randomization (MR) analysis, suggested that periodontitis may potentially have a causal effect on the risk of developing hypothyroidism [86].

In conclusion, there is an association between thyroid disease and periodontitis; however, further studies and investigations are needed to confirm the exact mechanisms by which they influence each other.

6. Obstructive Sleep Apnea Syndrome (OSA)

Apnea is the total cessation of airflow for at least 10 seconds, while hypopnea is a reduction in airflow for at least 10 seconds. Sleep apnea is divided into two main types:

- Central sleep apnea (CSA), where airflow stops due to a temporary lack of respiratory effort, is usually related to central nervous system issues such as poliomyelitis, spinal cord injury, or encephalitis [94].
- Obstructive sleep apnea (OSA), where airflow stops due to physical obstruction in the nasopharyngeal, oropharyngeal, or hypopharyngeal regions [94].

The severity of sleep apnea is measured using the Apnea-Hypopnea Index (AHI), calculated as the number of apneas and hypopneas per hour of sleep [94]. In adults, mild apnea is defined as an AHI of 5–15 episodes per hour, moderate as 15–30, and severe as more than 30 episodes per hour. In children, mild apnea is defined as 1–5 episodes per hour, moderate as 5–10, and severe as more than 10 episodes per hour [94].

OSA and periodontitis can be related because OSA, through intermittent hypoxia and the production of reactive oxygen species (ROS), activates inflammatory responses and proinflammatory cytokines such as IL-6, IL-1β, and C-reactive protein—the same mechanisms involved in periodontal disease [95–97]. These inflammatory mediators correlate with the severity of periodontal disease [95–98]. Moderate to severe OSA is often associated with higher levels of inflammatory mediators.

Mouth breathing, commonly seen in OSA, increases plaque accumulation and reduces saliva flow, further raising the risk of periodontal disease [95]. Intermittent hypoxia may also activate endothelial markers such as s-ICAM-1, increasing vulnerability to infection. OSA causes changes in the salivary microbiota, increasing the presence of bacteria responsible for gingivitis and periodontitis and leading to reduced microbial diversity [95,99,100].

OSA can indirectly contribute to periodontal disease by disrupting the oral microbiota and creating an environment that promotes inflammation and periodontal tissue degradation [95]. Additionally, gingivectomy and periodontal flap surgery have been shown to reduce the risk of OSA [95,101].

There is a complex and significant bidirectional relationship between OSA and periodontal disease, sharing risk factors, comorbidities, inflammatory pathways, and biomarkers [95]. Understanding this relationship will be fundamental for developing a multidisciplinary approach to treating oral and respiratory diseases based on strong scientific evidence. It may also enable early diagnosis of both conditions, allowing personalized and highly effective treatment for each patient [95].

Oral nurses, dentists, general practitioners, maxillofacial specialists, orthodontists, periodontists, and dental hygienists often encounter patients for various reasons and can play a key role in the early diagnosis of oral pathologies and related comorbidities. Their position in the healthcare chain is essential and highly valued, as early detection of chronic diseases—often possible through oral health professionals—significantly increases the chances of effective treatment [95].

7. Conclusions

Periodontitis is not merely a localized oral condition but is strongly associated with systemic diseases such as cardiovascular disease, diabetes mellitus, respiratory disorders, thyroid dysfunction, and obstructive sleep apnea. These associations are primarily mediated through shared pathophysiological and immunological mechanisms, including chronic inflammation, immune dysregulation, and microbial translocation. Understanding these connec-

tions underscores the importance of a comprehensive, interdisciplinary approach to patient care. Early detection, timely intervention, and preventive strategies—including lifestyle modifications—are crucial to addressing shared risk factors and improving both oral and systemic health outcomes. Given the substantial impact of periodontitis on patient well-being and the broader healthcare system, continued research is essential to further elucidate these relationships and support integrated care models.

Author Contributions

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