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Association between metabolic syndrome and periodontitis: The role of lipids, inflammatory cytokines, altered host response, and the microbiome

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1 | INTRODUCTION

Periodontitis is a “chronic inflammatory disease associated with dysbiotic plaque biofilms and characterized by a progressive destruction of the tooth supporting apparatus”.¹ Periodontitis affects 42.2% of the US population aged older than 30 years and 59.8% of those aged older than 65 years.² According to the World Health Organization, periodontitis is the major cause of tooth loss in adults.³ Periodontitis pathogenesis is multifactorial with environmental, microbial, and host involvement affecting disease outcomes. Many systemic conditions have been associated with periodontitis, including diabetes mellitus, cardiovascular disease, and metabolic syndrome.⁴⁻¹¹

Metabolic syndrome is a cluster of conditions that occur concomitantly and together they increase the risk of cardiovascular disease and double the risk of type 2 diabetes.¹²⁻¹⁵ Metabolic syndrome affects approximately 34% of the US population¹⁶ and 10% of US

adolescents.¹⁷ The prevalence of metabolic syndrome also increases with age and varies with ethnicity and gender.¹⁸ Several definitions of metabolic syndrome exist and differ slightly depending on the issuing agency. The most commonly utilized definition is provided by the National Cholesterol Education Program Adult Treatment Panel III. This definition requires that the individual has at least three of the following risk factors: (a) increased abdominal circumference, (b) low plasma levels of high-density lipoprotein cholesterol, (c) increased values for plasma triglycerides, (d) elevated blood pressure, and (e) elevated glucose levels.¹⁹ Prediabetes is also accepted as part of metabolic syndrome because it is associated with insulin resistance and is highly predictive of new-onset type 2 diabetes.²⁰

The predominant underlying risk factors for metabolic syndrome appear to be abdominal obesity and insulin resistance. Other associated conditions are physical inactivity, aging, and hormonal imbalance.²¹ Among the risk factors, visceral adiposity appears to be a

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primary trigger for most of the pathways involved in metabolic syndrome.²² The exact mechanisms behind this systemic response remain unclear, but there is evidence to suggest that the inflammatory state caused by metabolic syndrome is associated with endothelial dysfunction, which might contribute to the increased risk of cardiovascular disease and type 2 diabetes.²³⁻²⁵

Herein, we will focus on the association between metabolic syndrome and periodontitis; however, we will also include information on diabetes and cardiovascular disease since these two conditions are significantly intertwined with metabolic syndrome.

2 | METABOLIC SYNDROME AND PERIODONTITIS

2.1 | Association between metabolic syndrome and periodontitis

Considerable interest has been focused on the connection between periodontitis and metabolic syndrome because both of these conditions are associated with systemic inflammation and insulin resistance^{26,27} and they can potentially influence one another.

To date, there have been several longitudinal and cross-sectional studies as well as a few meta-analyses evaluating the relationship between these two conditions. The vast majority of the data point to an association between metabolic syndrome and periodontitis^{10,11,28-54} (Table 1). The three meta-analyses^{31,32,55} were performed utilizing different parameters, but each of them found an association between metabolic syndrome and periodontitis, with an odds ratio ranging from 1.38 to 1.99. The meta-analysis by Gobin et al⁵⁵ included 39 studies and demonstrated an association between periodontitis and metabolic syndrome with a crude odds ratio of 1.99 (95% confidence interval: 1.75-2.25) and an adjusted odds ratio of 1.46 (95% confidence interval: 1.31-1.61). The authors of this study also performed a subgroup analysis of different countries. The pooled odds ratio was 1.68 (95% confidence interval: 1.41-2) for Japan, 1.75 (95% confidence interval: 1.31-2.34) for the USA, 1.81 (95% confidence interval: 1.35-2.42) for Korea, and 2.29 (95% confidence interval: 1.53-3.41) for China.⁵⁵ The meta-analysis conducted by Daudt et al,³² which included 26 studies with radiographic and clinical examination, also found an association between metabolic syndrome and periodontitis with an odds ratio of 1.38 (95% confidence interval: 1.26-1.51). The authors went on to suggest that patients with metabolic syndrome are 38% more likely to have periodontitis.³² The systematic review/meta-analysis by Nibali et al³¹ included 20 studies (one longitudinal study) and a total of 36 337 subjects. The authors concluded that there is a positive association between metabolic syndrome and periodontitis with an odds ratio of 1.71 (95% confidence interval: 1.42-2.03). A critical review by Watanabe and Cho⁵⁶ also concluded that there is a positive association between metabolic syndrome and periodontitis. In addition, several animal studies utilizing different periodontitis models demonstrated that rodents with metabolic syndrome or obesity, as

a result of being fed a high-fat diet, also exhibited exacerbated periodontal bone loss.⁵⁷⁻⁵⁹

Evaluating the role of metabolic syndrome in periodontitis development and progression, Kaye et al⁴² and Iwasaki et al³⁵ performed longitudinal studies and concluded that metabolic syndrome increases the risk of development and progression of periodontitis (Table 1). In fact, Iwasaki et al³⁵ concluded that patients with metabolic syndrome were 2.6 times more likely to develop periodontitis. Likewise, the more components of metabolic syndrome an individual exhibited, the more prevalent and extensive the presentation of the periodontitis.^{35,38}

Until now, very little has been known about the potential gender predilection in the association between metabolic syndrome and periodontitis, and definitive conclusions cannot be made. Nonetheless, among the three relevant studies published, two concluded that there is a stronger association between metabolic syndrome and periodontitis in women,^{30,60} while the other study did not find a relationship between gender, metabolic syndrome, and periodontitis; however, Kushiyama et al⁴⁷ did comment that their small sample size could have influenced their results. As it relates to age, Minagawa et al⁹ suggested that metabolic syndrome and periodontitis are linked in the elderly population, which is consistent with the prevalence of metabolic syndrome and periodontitis increasing with age.^{61,62}

Although the vast majority of studies concluded that there is an association between metabolic syndrome and periodontitis, several studies found weak or no associations between these two conditions^{34,45,51,63-65} (Table 1). It is worth noting that most of these studies were cross-sectional in nature, with the longitudinal study spanning a period of 1 year; the study by Nascimento et al³⁴ was performed on a relatively young population (31 years of age), whose age bracket has a comparatively low prevalence of periodontitis and metabolic syndrome. Additionally, in a 3-year longitudinal study, Kobayashi et al⁶⁶ concluded that toothbrushing frequency is inversely related to the incidence of metabolic syndrome.

2.2 | Influence of periodontitis on metabolic syndrome

Some studies have suggested that periodontitis can affect systemic conditions.^{67,68} For example, periodontitis elevates the levels of several inflammatory mediators, such as C-reactive protein and interleukin-6.^{69,70} Moreover, periodontal treatment can decrease circulating levels of inflammatory mediators.^{71,72} Given this information, researchers have sought to evaluate the potential of periodontitis to affect metabolic syndrome.

The majority of studies concluded that periodontitis may contribute to the development or exacerbation of metabolic syndrome^{10,40,73} (Table 2). Nesbitt et al¹⁰ performed a cross-sectional study in 190 individuals evaluating periodontitis based on periodontal bone loss and concluded that periodontitis may contribute to the development of metabolic syndrome. Morita et al⁴⁰ conducted a

TABLE 1 The role of metabolic syndrome in periodontitis

Longitudinal studies						
Authors	Duration (y)	Age (y)	Sample size	Metabolic syndrome parameters	Periodontitis parameters	Results
Morita et al ⁴⁰	4	20 to 56	1023	BP, TG, HDL, TC, FPG, and BMI	PD (CPI)	Periodontitis was associated with a positive conversion of metabolic syndrome components
Bullon et al ⁴¹	3	20 to 44	188	Pregnancy, weight, BMI, BP, HbA1c, CRP, FPG, TG, TC, LDL, and HDL	Plaque, BOP, PD, recession	There is an association between periodontitis and metabolic syndrome
Iwasaki et al ³⁵	3	≥70	125	Abd obesity, BP, TG, HDL, and FPG	CAL	Metabolic syndrome may be a risk factor for periodontitis in older Japanese individuals
Kaye et al ⁴²	33		760	FPG, BP, TG, WC, and HDL	PD, CAL, ABL, tooth mobility	Metabolic syndrome may play a role in the development or worsening of periodontitis
Nascimento et al ³⁴	8 or 16		539	FPG, HDL, TG, WC, and BP	BOP, PD, CAL	Positive association between metabolic syndrome and periodontitis, when the multiple dimensions of both diseases were accounted in latent variables. When metabolic syndrome and periodontitis were treated as observed variables, no association was detected
Sakurai et al ⁴³	2	≥30	390	TG, HDL, BP, FPG, and WC	CPI	The prevalence of individuals with more positive metabolic syndrome components was higher in those with persistent/progressive periodontitis than in those with no/improved periodontitis
Tegelberg et al ⁴⁴	15		1964	WC, TG, HDL, BP, and FPG	PD and ABL	Metabolic syndrome was associated in an exposure-dependent manner with periodontitis
Adachi et al ⁴⁵	1	≥35	136	WC, TG, HDL, BP, and FPG	CPI	There were no associations between periodontitis and the development of metabolic syndrome
Cross-sectional/case-control studies						
Authors	Age of patients (y)	Number of patients	Metabolic syndrome parameters	Perio Parameters	Results	
Borges et al ⁶⁵	30 to 92	1315	BMI, dyslipidemia, BP and FPG	CPI	There were no associations between periodontitis and metabolic syndrome	
Shimazaki et al ²⁸	40 to 79	584	Abd obesity, TG, HDL, BP, and FPG	PD and CAL	Metabolic syndrome increases risk of periodontitis	
D'Aiuto et al ¹¹	≥17	13 677	WC, TG, HDL, BP, and insulin resistance	BOP, PD	Severe periodontitis is associated with metabolic syndrome in middle-aged individuals	
Khader et al ³⁷	≥25 or above	156	WC, TG, HDL, TC, BP, and FPG	PI, GI, PD, and CAL	Patients with metabolic syndrome displayed more severe and extensive periodontitis compared with subjects without metabolic syndrome	
Li et al ⁴⁶	37 to 78	208	Abd obesity, TG, HDL, BP, and FPG/or T2DM	CAL, PD, BOP, and PI	Patients with metabolic syndrome had poor periodontal conditions, and periodontitis was associated with metabolic syndrome, independent of other risk factors	

(Continues)

TABLE 1 (Continued)

Cross-sectional/case-control studies					
Authors	Age of patients (y)	Number of patients	Metabolic syndrome parameters	Perio Parameters	Results
Morita et al ²⁹	24 to 60	2478	WC, TG, HDL, TC, BP and FPG, HbA1c, and BMI	CPI	BMI, BP, TG, FPG, and HbA1c were significantly elevated in patients with PD of ≥ 4 mm. The adjusted odds ratio of the presence of periodontitis was 1.8 when the subjects with 2 positive components and without positive component were compared. And the odds ratio was 2.4 when the subjects with 3 or 4 positive components and without positive components were compared
Kushiya et al ⁴⁷	40 to 70	1070	Obesity, BP, HDL, TG, and FPG	CPI	The higher the number of metabolic syndrome components the higher the odds ratio of having more severe periodontitis
Andriankaja et al ³⁰	20 to >90	7431	Abd obesity, BP/or Med, TG, HDL and FPG/or Med	PD	The association between metabolic syndrome and periodontitis was significant in women. Abdominal obesity appeared to be the contributing metabolic factor for both genders
Benguigui et al ⁴⁸	35 to 74	276	WC, TG, HDL, BP, and FPG	PI, GI, PD, and CAL	There is a relationship between metabolic disturbances and periodontitis, with insulin resistance playing a central role
Han et al ⁴⁹	≥ 18	1046	Abd obesity, TG, HDL, BP, and FPG	BOP, PD, and calculus	Metabolic syndrome might be associated with periodontitis. The association was confounded by age, gender, and smoking. Metabolic syndrome with high glucose and hypertension showed higher impact on this association
Nesbitt et al ¹⁰	mean: 56.8 ± 12	190	BP, WC, TG, and FPG	ABL	Patients with severe periodontitis were approximately 2.5% times more likely to have metabolic syndrome
Timonen et al ⁶³	30 to 64	2050	Abd obesity Insulin resistance, BP, and dyslipidemia	PD	Metabolic syndrome was associated with PD ≥ 4 mm (adjusted risk ratio 1.19), and with pockets ≥ 6 mm (adjusted risk ratio 1.5)
Chen et al ³⁶	>18	253	WC, TG, HDL, TC, BP and FPG, or T2DM	PI, GI, and PDI	Moderate-severe periodontitis is associated with metabolic syndrome in patients undergoing hemodialysis
Kwon et al ²⁹⁷	≥ 19	7178	WC, TG, HDL, BP, and FPG	PD	Periodontitis is significantly associated with metabolic syndrome with an odds ratio of 1.55
Fukui et al ²⁹⁸	34 to 77	6,421	TG, HDL, BP, FPG, HDL, BP, and obesity	PD and CAL	Periodontal status, particularly in individuals suspected to have untreated periodontal infection, is significantly associated with metabolic syndrome
Furuta et al ⁶⁰	40 to 79	2370	WC, TG, BP HDL, and FPG	PD, CAL, and BOP	Gender differences appear to exist in the association between periodontitis and metabolic syndrome. Metabolic syndrome might have a stronger association with periodontitis in females compared with males

(Continues)

TABLE 1 (Continued)

Cross-sectional/case-control studies					
Authors	Age of patients (y)	Number of patients	Metabolic syndrome parameters	Perio Parameters	Results
Sora et al ³⁹	26 to 87	283	Abd obesity, BP, HDL, TG, and FPG (OGTT)	Plaque, PD, CAL, and BOP	Metabolic syndrome is associated with the extent of severe periodontitis in this Gullah population with type 2 diabetes
LaMonte et al ⁶⁴	50 to 79	657	Abd obesity, BP or Med, TG, FPG or Med and HDL	ABL, PD, and CAL	A consistent association between metabolic syndrome and measures of periodontitis was not seen in this cohort of postmenopausal women
Thanakun et al ³³	35 to 76	125	WC, TG, HDL, BP, and FPG	BOP, PD, and CAL	Severe periodontitis was associated with metabolic syndrome (odds ratio 3.6) when 4-5 metabolic syndrome components were analyzed the odds ratio increased to 5.49 in this Thai population
Minagawa et al ⁹	≥80	234	WC, FPG, BP, and dyslipidemia	PD and CAL	Metabolic syndrome was associated with the presence and severity of periodontitis (crude odds ratio 2.24)
Chen et al ²⁹⁹	23 to 58	303	Abd obesity, BP, TG, HDL, and FPG	CPI	The prevalence of metabolic syndrome was sufficiently high to be a medical concern, and was associated with periodontitis
Gomes-Filho et al ⁵⁰	24 to 89	419	WC, TG, HDL, BP, and FPG	PD, CAL, and BOP	Periodontitis is associated with metabolic syndrome
Musskopf et al ⁵¹	18 to 81	363	WC, TG, HDL, BP, and FPG	PI, GI, PD, CAL, and BOP	There is a weak association among metabolic syndrome and periodontitis. The association is observed in the age group of 41-60 y
Jaramillo et al ⁵²		651	TG, HDL, BP, BMI, and glucose tolerance	GI, PI, PD, CAL, and BOP	There is a positive association between metabolic syndrome and periodontitis. The adjusted odds ratio is 2.72. Glucose sensitivity is a strongly associated component
Kikui et al ⁵³	mean: 66.4	1856	BP and/or Med, HDL, TG and/or Med, FPG/and Abd obesity	CPI	Metabolic syndrome and lower HDL cholesterol are associated with periodontitis. Subjects with 2 or more metabolic syndrome components had a significantly higher prevalence of periodontitis
Kim et al ³⁰⁰	50 to 94	5078	BMI, WC, BP, FPG, HDL, and TG	PD and CAL	Increasing the severity of periodontitis was associated with the risk of prevalent metabolic syndrome in Korean adults
Pham et al ³⁸	mean: 57.8 ± 5.7	412	BMI, WC, HDL, BP and FPG	PI, GI, PD, CAL, and BOP	More severe and extensive periodontitis was found in metabolic syndrome participants and increased with number of metabolic syndrome components. Participants with higher periodontal parameters had a higher risk of metabolic syndrome
Campos et al ⁵⁴		122 with metabolic syndrome and 366 controls	BP, TGs and LDL and/or WC	PI, BOP, PD, and CAL	There is an association between metabolic syndrome and periodontitis

Abbreviations: Abd, abdominal; ABL, alveolar bone level; BMI, body mass index (kg/m²); BOP, bleeding on probing; BP, blood pressure; CAL, clinical attachment level; CPI, community periodontal index; CRP, C-reactive protein; FPG, fasting plasma glucose; GI, gingival bleeding index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Med, medication; OGTT, oral glucose tolerance test; PD, probing depth; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

TABLE 2 Effect of periodontitis on metabolic syndrome

Authors	Cross-sectional (CS) or longitudinal (L)	Duration	Age of patients (y)	Number of patients	Metabolic syndrome parameters	Periodontitis parameters	Results
Kushiyama et al ⁴⁷	CS		40 to 70	1070	Obesity, BP, HDL, TG, and FPG	CPI	The higher the number of metabolic syndrome components, the higher the odds ratio of having more severe periodontitis
Morita et al ⁴⁰	L	4 y	20 to 56, mean: 37.3	1023	BP, TG, HDL, TC, FPG, and BMI	CPI	Periodontal pockets were associated with a positive conversion of metabolic-syndrome components
Nesbitt et al ¹⁰	CS		mean: 56.8 ± 12.7	190	BP, WC, TG, and FPG	ABL	Alveolar bone loss is associated with metabolic syndrome
Lopez et al ⁷³	L	1 y	35 to 65	165	Abd obesity, TG, HDL, BP, and FPG	≥4 teeth with ≥ 4mm and CAL of ≥ 3mm	Reduction of periodontal inflammation either with scaling and root planing and systemic antibiotics or with plaque control and subgingival scaling reduces CRP levels after 9 mo in patients with metabolic syndrome
Kim et al ³⁰⁰	CS		50 to 94	5078	BMI, WC, BP, FPG, HDL, and TG	PD and CAL	Increasing the severity of periodontitis was associated with the risk of prevalent metabolic syndrome in Korean adults

Abbreviations: Abd, abdominal; ABL, alveolar bone level; BMI, body mass index (kg/m²); BP, blood pressure; CAL, clinical attachment level; CPI, community periodontal index; CRP, C-reactive protein; FPG, fasting plasma glucose; HDL, high-density lipoprotein; PD, probing depth; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

longitudinal study on 1023 adults and concluded that deeper periodontal pockets are associated with a positive conversion of one or more metabolic components during a 4-year period (odds ratio: 1.6; 95% confidence interval: 1.1-2.2). Moreover, Lopez et al⁷³ suggested that reduction of periodontal inflammation reduces C-reactive protein levels in patients with metabolic syndrome.

2.3 | Periodontal microbiome changes in patients with metabolic syndrome

In recent years, considerable attention has been given to the microbiome. Metabolic diseases alter the gut microbiome (reviewed by Karlsson et al⁷⁴), and it is well known that the oral microbiome varies significantly between healthy and periodontitis patients.⁷⁵ Additionally, alterations in the gut microbiome have been linked to obesity and metabolic syndrome.⁷⁶ Furthermore, obesity can alter the oral microbiome of individuals with type 2 diabetes⁷⁷ and it can reduce microbial diversity in the distal gut.^{78,79} More specifically, individuals with lower microbiome diversity have marked overall adiposity, insulin resistance, and dyslipidemia compared with those with high bacterial richness.⁷⁹ Tam et al⁷⁷ evaluated 17 individuals with severe periodontitis and concluded that oral microbial composition varies significantly between obese (body mass index ≥ 30) and nonobese individuals with type 2 diabetes. This study implied that obesity was associated with a reduction in species diversity in the oral cavity.

2.4 | We also hypothesized that the oral microbiome is altered in metabolic syndrome patients compared with healthy patients

To test this hypothesis, we performed microbial 16S rDNA profiling of unstimulated saliva from healthy individuals and individuals with metabolic syndrome, with and without periodontitis. The primary objective was to make comparisons between two groups, categorized as metabolic syndrome and systemically healthy (two-group analysis: healthy vs metabolic syndrome). The secondary objective was to stratify the metabolic syndrome patients by periodontal health status (four-group analysis: healthy vs healthy* vs metabolic syndrome healthy periodontium vs metabolic syndrome periodontitis). Note: three healthy subjects presented with an elevated systolic and/or diastolic blood pressure reading (stage I hypertension values, according to the American Heart Association) and thus were stratified into a healthy* group.

More specifically, this study consisted of a total of 22 subjects (12 metabolic syndrome and 10 healthy individuals). The 12 metabolic syndrome patients also had diabetes. Metabolic syndrome subjects were further stratified by periodontal status. Downstream analyses included alpha diversity, linear discriminant analysis effect size, and beta diversity using principal coordinate analysis. Kruskal-Wallis and linear discriminant analysis were used for evaluating statistical significance between healthy and metabolic syndrome microbial communities.

2.5 | Results

The saliva samples yielded 2 270 978 assigned reads, including 1 155 315 single species, 1 088 960 multispecies, and 24 866 novel species reads. At the species level, 573 total species were

represented as operational taxonomic units: 330 single species, 145 multispecies, and 98 novel species. Detailed data can be found at http://www.homd.org/ftp/publication_data/20170412/qiime_results/cd_mc10/taxa_plots/taxa_summary_plots/bar_charts.html.

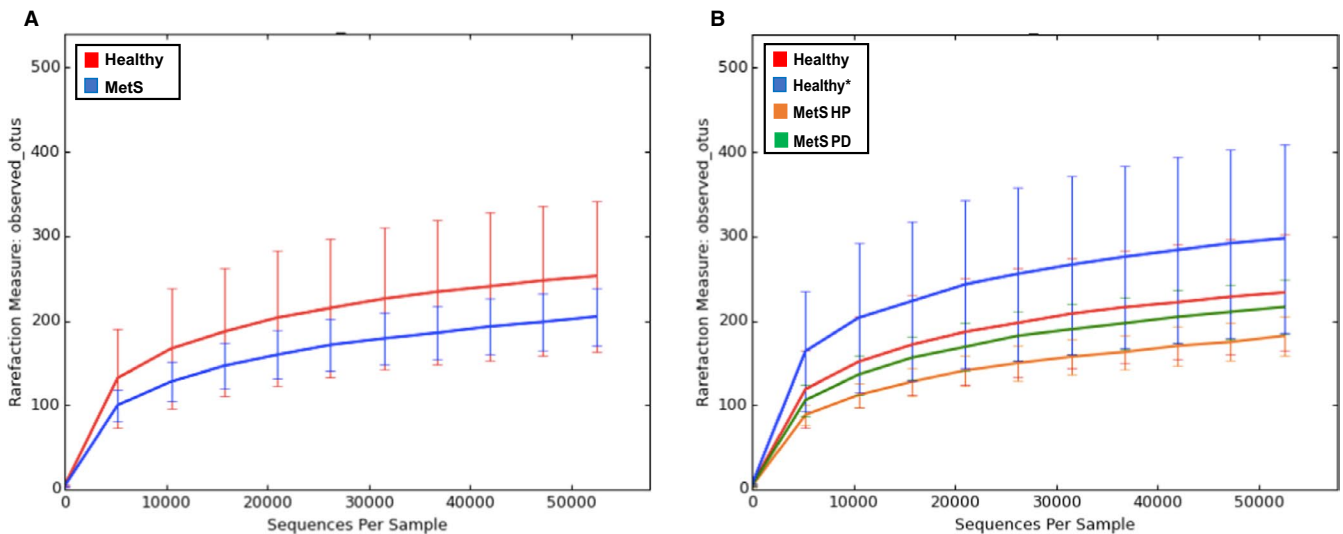


FIGURE 1 Rarefaction plots show distinct levels of alpha diversity between healthy and metabolic syndrome subjects. The two-group analysis rarefaction plot (A) represents the rarefaction curves of the healthy and metabolic syndrome subjects. Both curves show similar species richness and the curves plateau as the number of sequences rise per sample. The four-group analysis rarefaction plot (B) shows similar alpha diversity in terms of species richness and both begin to plateau and the curves of all four groups begin to plateau as the number of sequences rises per sample. MetS, metabolic syndrome; MetS HP, metabolic syndrome with healthy periodontium; MetS PD, metabolic syndrome with periodontitis; OTUs, operational taxonomic units

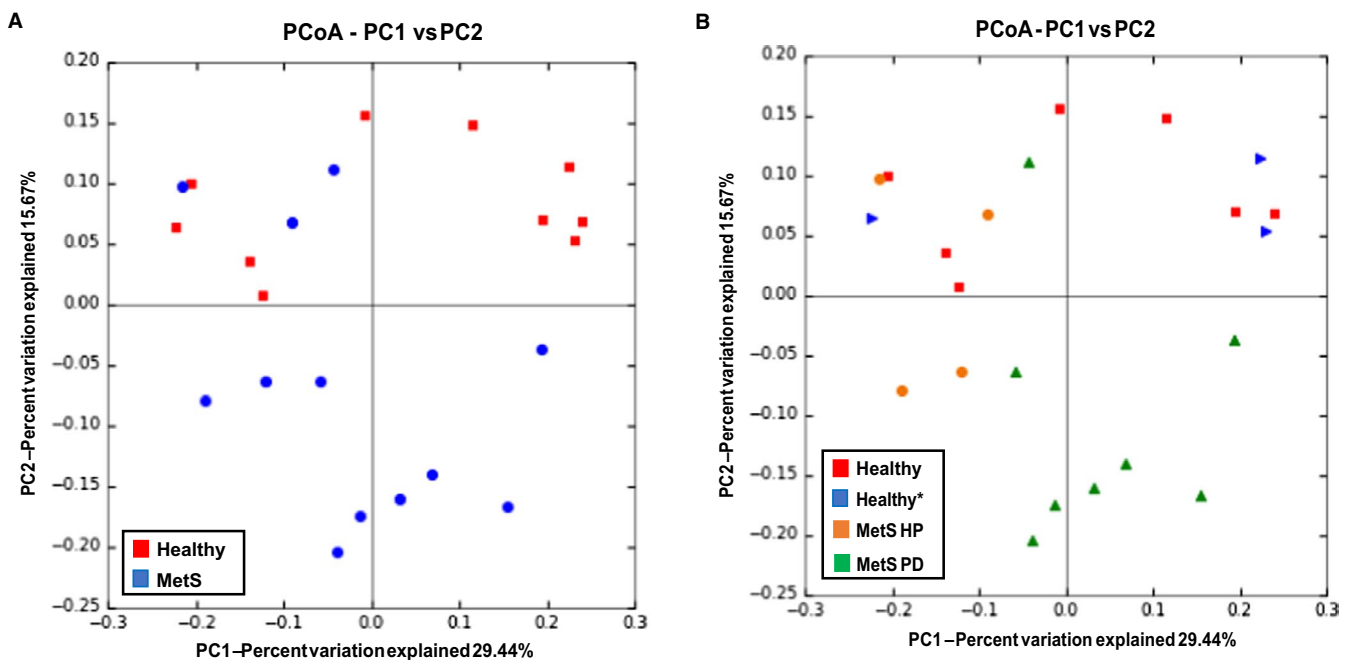


FIGURE 2 Principal coordinate analysis (PCoA) for all groups show the relative relatedness within groups. A two-dimensional view of the three-dimensional PCoA plot, derived from UniFrac as a distance metric, is shown in A, representing beta diversity for the two-group analysis. It can be appreciated that the two groups appear to be more related within group than between group as evidenced by clusters. A two-dimensional view of the three-dimensional PCoA plot, derived from UniFrac as a distance metric, is shown in B, representing beta diversity for the four-group analysis. No conclusive result regarding beta diversity can be observed from these plots. MetS, metabolic syndrome; MetS HP, metabolic syndrome with healthy periodontium; MetS PD, metabolic syndrome with periodontitis

Evaluating the alpha diversity, the rarefaction plot for the two-group analysis of metabolic syndrome vs healthy subjects (Figure 1A), and for the four-group analysis of healthy vs healthy* vs metabolic syndrome healthy periodontium vs metabolic syndrome periodontitis using observed operational taxonomic units (Figure 1B), exhibits curves plateauing with the increased sequences sampled, indicative of adequate alpha diversity in terms of species richness. It is clear that the healthy salivary microbiome is more diverse compared with that found in the metabolic syndrome subjects.

Evaluating beta diversity, three-dimensional principal coordinate analysis plots were generated (Figure 2). The two-group analysis (Figure 2A) suggests that subjects within each group show more relatedness to one another than to a subject of the opposite group. A less organized pattern is demonstrated in the four-group analysis plot and no conclusive result regarding beta diversity can be observed from this plot (Figure 2B).

Next, we evaluated the phylogenetic relationship of taxa among the groups. A cladogram was generated representing the phylogenetic relationship of taxa associated with the healthy and metabolic syndrome groups (Figure 3). At the species level, taxa significantly associated with healthy patients showed relatedness. The cladogram in Figure 3B represents the taxonomic relationship between taxa significantly associated with the four groups analyzed. Phylogenetically related taxa at the species level are significantly associated with health (specifically, the taxa stemming from the class Betaproteobacteria from the phylum *Proteobacteria*), healthy* (including taxa stemming from the phylum SR1, class *Flavobacteria*, and order *Corynebacteriales*), and metabolic syndrome with periodontitis (including taxa stemming from the phylum *Tenericutes* and phylum *Spirochaetes*, as well as the order *Coriobacteriales*).

In summary, the 16S rDNA sequence analyses support the hypothesis that the salivary bacterial profile is altered in metabolic syndrome patients compared with healthy patients. Despite a small sample size, the healthy group was more diverse than the metabolic syndrome group (Figures 1 and 2). When further stratified, the metabolic syndrome healthy periodontium and metabolic syndrome periodontitis subject groups displayed comparatively different microbial profiles with both one another and with healthy subjects (Figure 3). Additionally, the metabolic syndrome periodontitis group displayed a large effect size difference and a greater abundance of two of the three classic periodontal "red complex" pathogens,⁸⁰ namely, *Tannerella forsythia*, the phylum *Spirochaetes*, and genus *Treponema*. However, a significant effect size difference was not detected between the groups for *Porphyromonas gingivalis*. Based on our study, additional research with an increased subject population is warranted to further advance these novel findings.

2.6 | Lessons from animal models: the role of dyslipidemia

To date, a few in vivo and in vitro studies have highlighted the role of dyslipidemia (in a high-fat diet model) in the compounding effect

of metabolic syndrome on periodontitis^{57-59,81} (Table 3) and several studies have evaluated the role of impaired glucose in periodontitis; the latter are discussed in the Diabetes section of this review.

Amar et al⁵⁷ demonstrated that mice fed a high-fat diet, but not presenting with diabetes, had 40% more periodontal bone loss and higher titers of *Po. gingivalis* compared with the control mice in a *Po. gingivalis* bacterial colonization model (silk ligature and *Po. gingivalis* oral inoculation). Although this study did not evaluate metabolic syndrome markers, these mice were obese and the study utilized a well-known metabolic syndrome model.⁵⁷ Subsequently, utilizing the same metabolic syndrome model, Li et al⁵⁹ demonstrated that mice fed a high-fat diet developed metabolic syndrome, as determined by obesity, hyperinsulinemia, insulin resistance, and dyslipidemia. In this study, metabolic syndrome led to a significant increase in osteoclastogenesis and periodontal bone loss. Moreover, lipopolysaccharide-induced periodontitis exacerbated inflammatory cytokine expression (interleukin-6, monocyte chemoattractant protein1, RANKL, and macrophage colony-stimulating factor), osteoclastogenesis, and periodontal bone loss.⁵⁹ In vitro studies utilizing osteoblasts derived from obese New Zealand mice demonstrated a decrease in cell proliferation and an increase in osteoblast apoptosis after *Po. gingivalis* exposure compared with control mice.⁸² Additionally, obese Zucker rats with metabolic syndrome had a statistically significant increase in *Aggregatibacter actinomycetemcomitans*-lipopolysaccharide-induced periodontal bone loss compared with the nonobese, non-metabolic syndrome group. Moreover, statin, a cholesterol-lowering drug often prescribed to individuals with metabolic syndrome,⁸³ alleviated periodontal bone loss in both groups, also pointing to dyslipidemia as a potential exacerbator of periodontal inflammation.⁸⁴

To further establish the role of lipids in periodontitis, Li et al⁵⁹ demonstrated that fatty acids (eg, palmitic acid) amplified the lipopolysaccharide-mediated expression of markers involved in periodontitis, such as interleukin-1-alpha, interleukin-1-beta, C-X-C motif chemokine ligand 10, cluster of differentiation 86, colony stimulating factor 2, monocyte chemoattractant protein 1, toll-like receptor, tumor necrosis factor-alpha, and cluster of differentiation 14 in vitro.⁵⁹ In addition, in vitro studies performed in macrophages showed a statistically significant upregulation of cluster of differentiation 36, a major fatty acid receptor, upon treatment with lipopolysaccharide plus palmitate in comparison with those macrophages treated with lipopolysaccharide or palmitate alone.⁸¹ Periodontitis and metabolic syndrome independently increased cluster of differentiation 36 levels significantly, and when metabolic syndrome and periodontitis were developed concurrently, there was an additive effect. Cluster of differentiation 36 expression in periodontal tissues was also positively correlated with osteoclastogenesis.

In summary, human studies and animal models demonstrate an association between metabolic syndrome and periodontitis, and metabolic syndrome can alter the oral microbiome and potentiate the deleterious effects of periodontitis.

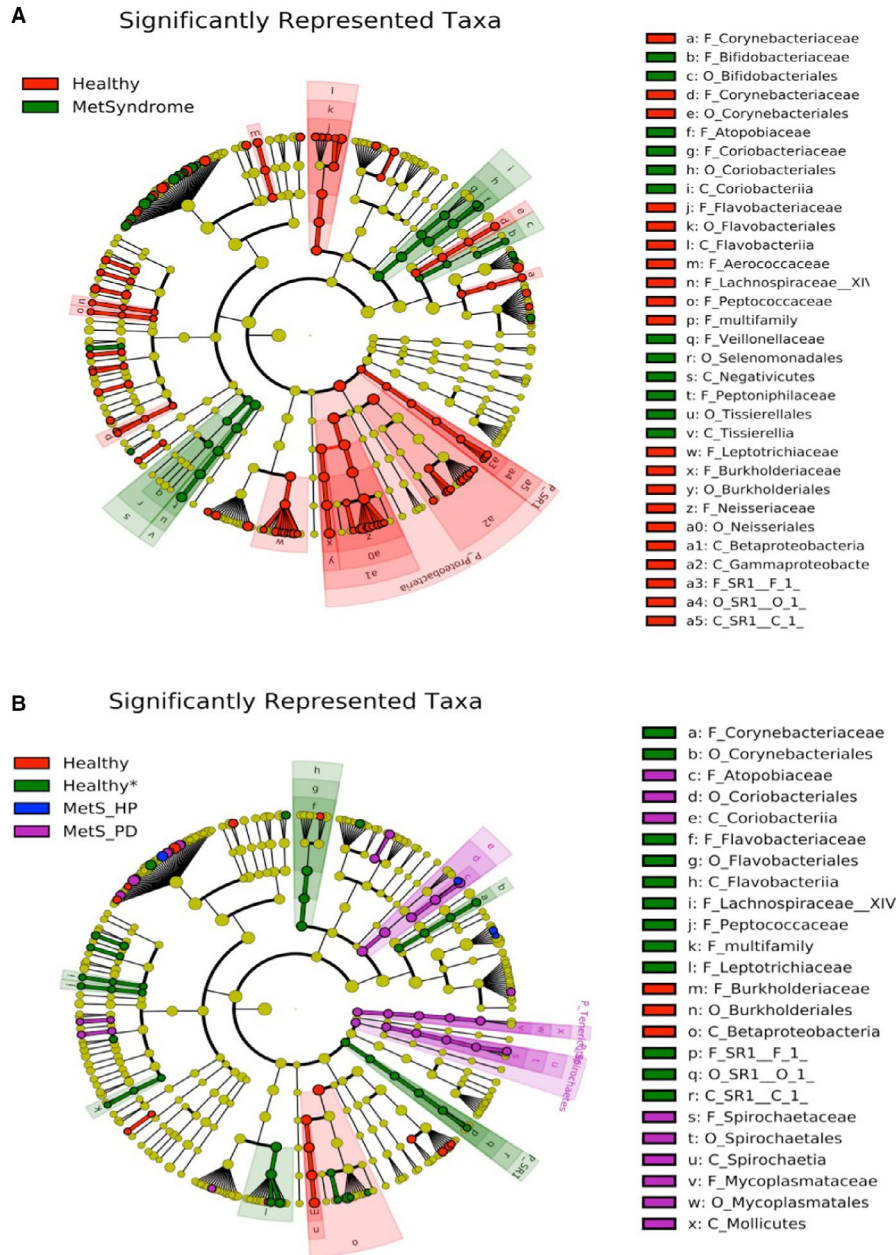


FIGURE 3 The cladograms show the phylogenetic relationship and taxonomic groupings of the taxa significantly associated with different subject groups. A, The phylogenetic relationship and taxonomic groupings of the taxa significantly associated with healthy and metabolic syndrome (MetSyndrome) subjects. Dots of red (health) and green (metabolic syndrome) represent significantly associated taxa to the labeled group and the size of the dot corresponds to relative abundance. At the outer edge of the cladogram, a letter is listed to represent this taxon and corresponds with the legend on the right. A strong association between taxa stemming from the phylum *Proteobacteria* and phylum *SR1* and health is shown. Taxonomic relationships are shown in clusters of green for taxa significantly associated with the metabolic syndrome group. B, The phylogenetic relationship and taxonomic groupings of the taxa significantly associated with healthy (red), healthy* (green), metabolic syndrome with healthy periodontium (MetS_HP; blue), and metabolic syndrome with periodontitis (MetS_PD; purple). Colored dots represent significant taxa for the denoted group and the size of the dot corresponds to relative abundance. At the outer edge of the cladogram, letters are used to represent the significant taxa, listed in the legend on the right side of the figure. A strong association is shown between taxa stemming from the phyla *Tenericutes* and *Spirochaetes* and order *Coriobacteriia* for metabolic syndrome with periodontitis subjects; a strong association is shown between taxa stemming from the phylum *SR1* and healthy* subjects, and taxa associated with the phylum *Proteobacteria* and healthy subjects

3 | DIABETES

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin

action, or both. Approximately 415 million people in the world live with diabetes and this number is expected to increase to 642 million by 2040.⁸⁵ In the USA, diabetes is present in 13% of adults. Diabetes increases with age, affecting 26.8% of individuals aged 65 years or

TABLE 3 Metabolic syndrome: animal data

Authors	Duration of the study (wk)	Number of samples	Metabolic syndrome parameters	Periodontitis parameters	Results
Amar et al ⁵⁷	16	N/A	Not evaluated	ABL	Mice with <i>P. gingivalis</i> -induced periodontitis and diet-induced obesity had a significantly higher level of alveolar bone loss compared with the lean controls
Watanabe et al ¹⁸⁵	13	28	FPG and fasting insulin levels	ABL	High-fat/periodontitis rats developed more severe insulin resistance compared with high-fat/control, low-fat/periodontitis or low-fat/control rats as measured by fasting insulin levels and homeostasis model assessment analysis
Ohnishi et al ³⁰¹	20		insulin resistance	ABL	Oxidative stress causes alveolar bone loss in a metabolic syndrome mouse model with type 2 diabetes
Jin et al ⁵⁸	4	44 (22/group)	FPG, TG, FFA, and TC	ABL	Simvastatin inhibited LPS-induced bone loss and periodontal inflammation in rats with metabolic syndrome
Li et al ⁵⁹	16	14	TC, TG, and FFA	ABL	Saturated fatty acid may play a role in metabolic syndrome-associated periodontitis by enhancing LPS-induced inflammatory cytokine expression
Lu et al ⁸¹	16	28 (14/group)	FPG, TG, FFA, TC, and insulin	ABL	CD36 expression is upregulated in mice with periodontitis and metabolic syndrome and is involved in gene expression in macrophages stimulated by palmitate and LPS

Abbreviations: ABL, alveolar bone level; CD36, cluster of differentiation; CPI, community periodontal index; FFA, free fatty acid; FPG, fasting plasma glucose; LPS, lipopolysaccharide; N/A, not applicable; TC, total cholesterol; TG, triglycerides.

older.⁸⁶ Of all diabetes cases, type 2 diabetes accounts for approximately 90%-95% of those with diabetes and encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency.⁸⁷ Type 2 diabetes affects more than 380 million people worldwide, representing 8.8% of individuals aged 20-79 years.⁸⁸

The chronic hyperglycemia caused by type 2 diabetes is associated with long-term damage and disabling and life-threatening health complications, such as cardiovascular disease, neuropathy, and nephropathy.⁸⁹⁻⁹² Periodontitis is highly likely to develop in individuals with diabetes and constitutes the sixth most frequent complication of diabetes.⁹³ The reverse is also true, as individuals with periodontitis are more likely to develop diabetes, thus establishing a "two-way" relationship between the two conditions.^{94,95} Since much is known about the two-way relationship between these two conditions, this review will emphasize the role of diabetes on the periodontal microbiome.

3.1 | Role of type 2 diabetes in periodontitis

The association between diabetes and periodontitis has long been established, with most studies showing that poorly controlled diabetes affects periodontitis development and progression.⁹⁶⁻¹¹⁶ The odds ratio for patients with diabetes having periodontitis varies;

Emrich et al¹⁰⁵ reported an odds ratio of 2.81 and Tsai et al¹⁰⁰ reported that the odds ratio in individuals with better controlled diabetes is 1.56. Nelson et al,¹¹² having evaluated subjects with type 2 diabetes, concluded that the rate of periodontitis is 2.6 times higher in subjects presenting with type 2 diabetes compared with those without it.¹¹² Along those lines, several studies have shown that uncontrolled type 2 diabetes is associated with periodontitis progression; however, controlled type 2 diabetes or altered glycemic levels without diabetes are not associated with periodontitis.^{98,109,117-119} In addition, the longer duration of diabetes appears to correlate with periodontitis severity.¹²⁰

Patients with diabetic retinopathy appear to have more severe periodontitis compared with those without retinopathy.¹²¹ Interestingly, despite the higher prevalence and severity of periodontitis in subjects with diabetes, Newton et al,¹²² evaluating 46 132 electronic charts of patients with periodontitis with and without diabetes, concluded that individuals with diabetes had significantly more periodontitis treatment compared with normoglycemic individuals.

The mechanisms by which diabetes affects periodontitis have been studied in animals and are described below. However, analyzing periodontal tissues and/or gingival crevicular fluid, it has been noted that interleukin-1-beta is increased and that diabetes also increases advanced glycation end products and oxidative stress.¹²³⁻¹²⁵

3.2 | Role of periodontitis in diabetes

Chronic subclinical inflammation plays a role in the pathogenesis of type 2 diabetes.^{126,127} Given that periodontitis leads to subclinical inflammation,¹²⁸ many studies have evaluated the role of periodontitis on glycemic levels, as well as on the incidence of type 2 diabetes and diabetes complications.¹²⁹⁻¹³⁶ Periodontitis is associated with hemoglobin A1c progression in individuals with diabetes.¹³⁷ Additionally, deeper probing depths are more closely associated with increased hemoglobin A1c levels.^{68,132,138,139} Even in healthy individuals, periodontitis can worsen glycemic control.¹⁴⁰⁻¹⁴⁴

Regarding the development of type 2 diabetes, most studies have linked periodontitis to a higher probability of developing diabetes.^{133,145,146} For instance, Winning et al¹⁴⁷ concluded that the hazard ratio of developing type 2 diabetes in individuals with moderate-severe periodontitis is 1.69. Another study, which evaluated 22 299 patient charts with a 5.47-year mean follow-up, concluded that patients with periodontitis requiring surgery are at a higher risk of developing type 2 diabetes.¹³³ Another 5-year study, utilizing tooth loosening as a proxy for periodontitis, also identified a correlation between incident diabetes and tooth loosening.¹⁴⁸ On the other hand, some studies were unable to find an association between type 2 diabetes incidence and periodontitis.^{129,149} For instance, Kebede et al¹²⁹ followed 2047 subjects for a period of 11.1 years; although individuals with incident cases of diabetes tended to have poorer periodontal status, once the data were adjusted for age, gender, and central adiposity, the correlation no longer existed. This contradictory result could have been in part influenced by the population evaluated (Caucasian), a partial periodontal evaluation, examination of hemoglobin A1c at only two data points, and 21% of subjects reporting having had periodontal treatment during the study period.

Severe periodontitis is associated with a higher presence of diabetes-related complications, including retinopathy, foot ulcerations, and renal and cardiovascular complications.^{134,135,138,150-157} For example, Saremi et al¹³⁴ evaluated Pima Indians in a long-term study with a median follow-up of 11 years, and concluded that periodontitis is a strong predictor of mortality from ischemic heart disease and diabetic nephropathy.

3.3 | Role of periodontal treatment on glycemic control

Given the role of periodontitis in diabetes, studies have sought to understand whether periodontal treatment would ameliorate glycemic control. Unfortunately, to date, the results are conflicting in this regard.^{136,158-165} These contradictory results could be, at least in part, attributed to differences in the treatment rendered, the duration of the study (1-12 months), and because a proxy for periodontitis (dental insurance data) was utilized.

Among the studies concluding that periodontal treatment lowered hemoglobin A1c levels¹⁵⁸⁻¹⁶³ is a large study conducted by D'Aiuto et al¹⁵⁸ presenting a 12-month follow-up. In agreement with

the results of that study, Spangler et al¹⁶³ evaluated medical records and dental insurance data as a proxy for periodontitis over a period of 5 years, and also concluded that patients who received periodontal treatment had slightly lower hemoglobin A1c levels compared with those who did not receive treatment. However, periodontal parameters were not considered in this study, only insurance data.

Conversely, several studies did not find a relationship between periodontitis treatment and hemoglobin A1c levels.^{136,161,164,165} These findings were probably attributable to the short-term (3-month) follow-up, which may not have been sufficient to demonstrate a change in hemoglobin A1c levels.

Given the differences in periodontal treatment in various studies, the inability to restrict patients from obtaining periodontal treatment for an extended period,^{34,43} and the short-term follow-up, more studies are needed to determine if periodontal treatment affects glycemic control.

3.4 | Lessons from animal models: interactions between diabetes and periodontitis

To date, different animal models of type 1 diabetes and type 2 diabetes have been utilized with the aim of understanding the mechanisms by which diabetes and periodontitis affect one another. Herein, we briefly discuss some of these findings.

When evaluating the role of diabetes in periodontitis, studies have shown that diabetes increases periodontal bone loss,¹⁶⁶⁻¹⁷⁰ but also that the severity of periodontal breakdown corresponds to the severity of diabetes.¹⁷¹ Moreover, diabetes without periodontitis leads to periodontal alterations, such as a decrease in bone crest height and an increase in inflammatory cells and osteoclast numbers.^{172,173} The exact mechanisms by which diabetes affects periodontitis are not fully understood; however, it is known that diabetes worsens periodontitis in part by (a) increasing the inflammatory response,^{166,170} (b) enhancing cell apoptosis,¹⁷⁴⁻¹⁷⁶ (c) increasing osteoclast formation, (d) increasing bone resorption,^{168,174} and (e) suppressing bone formation.¹⁷⁷ These changes can be partially explained because diabetes (a) increases advanced glycation end products and their respective receptors (receptor for advanced glycation end products),^{4,178} (b) increases toll-like receptor 2 and toll-like receptor 4 expression,^{179,180} (c) alters the RANKL ratio,¹⁸¹ and (d) leads to mitochondrial dysfunction,^{182,183} which in turn enhances local and systemic oxidative damage.¹⁷⁵

The reverse is also true: most animal studies have also concluded that periodontitis affects diabetes. For instance, rodents with induced periodontitis are more glucose intolerant,¹⁸⁴ have more severe fasting insulin levels,¹⁸⁵ and have increased pancreatic beta-cell failure.¹⁸⁶ Periodontitis even alters glucose metabolism in rodents with prediabetes.¹⁸⁷ The mechanisms by which periodontitis affects diabetes are not entirely clear but include increased circulating levels of different cytokines, such as interleukin-1-beta, tumor necrosis factor-alpha, and adiponectin, as well as increased adipose tissue inflammation.^{184,185,188}

Taken together, animal studies also point to the bidirectional role of diabetes and periodontitis and shed some light on the mechanism by which these conditions lead to a pro-inflammatory response. However, further studies are needed for a more comprehensive understanding of this relationship.

3.5 | Type 2 diabetes and the microbiome

Considerable attention has been given to the ability of chronic conditions to alter the microbiome. For instance, individuals with type 2 diabetes or obesity have a modified gut microbiome.^{74,189-191} Conversely, mice treated with *Enterobacter cloacae* B29, which was isolated from the intestines of obese patients with diabetes, also developed obesity and insulin resistance,¹⁹² showing that microbes can also directly induce diabetes-related symptoms. Furthermore, intervening with the flora or modulating bacterial-mucosal immunity-inflammation may alleviate type 2 diabetes.¹⁹³ Given the association between type 2 diabetes, periodontitis, and the changes that have been observed in the gut microbiome in individuals with type 2 diabetes, additional attention has been given to microbiome changes in the periodontium of individuals with type 2 diabetes.

3.6 | Diabetes affecting the subgingival microbiome

Type 2 diabetes alters the subgingival and salivary bacterial profile of individuals (Table 4) by decreasing diversity and richness.¹⁹⁴⁻¹⁹⁹ This is consistent with data observed within the gut microbiome.^{74,189-191,200} When evaluating the subgingival microbiome, not only is the diversity decreased in individuals with type 2 diabetes, but when these individuals are further divided by adequate or inadequate glycemic control, there is a notable further decrease in the microbiome diversity in those with inadequate glycemic control (hemoglobin A1c \geq 8%).²⁰¹ By contrast, a study performed by Tam et al⁷⁷ evaluated the salivary microbiome of 17 individuals with periodontitis and type 2 diabetes, but the authors were unable to determine statistically if glycemic control could also change the oral microbiota. However, it was noted that, in individuals with type 2 diabetes, the microbial composition varied significantly between obese (body mass index \geq 30 kg/m²) and nonobese individuals with type 2 diabetes, with obesity reducing the diversity of species in the oral cavity.⁷⁷

Although the diversity of the subgingival and supragingival microbiome decreases when subjects with type 2 diabetes are compared with normoglycemic individuals, the bacterial shift in individuals with periodontitis is less prominent in type 2 diabetes subjects than in normoglycemic individuals.^{195,196,202}

There is not much consensus regarding the specific differences in the microbiome (Table 4). However, individuals with diabetes had a higher total taxa of *Saccharibacteria* (TM7), *Aggregatibacter*, *Neisseria*, *Gemella*, and *Eikenella*.¹⁹⁴ Matsha et al¹⁹⁷ noted that *Fusobacterium*

and *Actinobacteria* are more abundant in subjects with diabetes. Furthermore, in subjects with type 2 diabetes and bleeding on probing, there was an increase in the abundance of *Bacteroidetes* (*Po. gingivalis* belongs to this phylum).¹⁹⁷

Targeted studies utilizing DNA-DNA hybridization technology or PCR assays evaluated the presence of specific bacterial taxa or groups of bacteria but no consensus was reached. Aemaimanan et al²⁰³ and Babaev et al²⁰⁴ reported that individuals with poorly controlled type 2 diabetes have higher levels of red complex bacteria (*Po. gingivalis*, *Treponema denticola*, and *Ta. forsythia*).^{203,204} On the other hand, Rodríguez-Hernández et al²⁰⁵ found a decrease in red complex bacteria in Mexican individuals with type 2 diabetes compared with normoglycemic individuals with periodontitis. However, individuals with type 2 diabetes and periodontitis had higher levels of the yellow and orange complexes.²⁰⁵

There are also some contradictions among different studies when analyzing individual bacterial species. For instance, *Po. gingivalis* was increased in individuals with periodontitis and type 2 diabetes,^{203,204,206,207} but decreased in other individuals.^{194,208,209} Some studies found that the levels of *Tr. denticola* were higher in patients with type 2 diabetes compared with normoglycemic controls,^{203,204,210} while no difference was observed in other studies.^{206,208}

When type 2 diabetes and periodontitis were evaluated in individuals who smoke, the subgingival microbiome of smokers with type 2 diabetes had lower diversity, higher levels of gram-negative facultative anaerobes, and lower levels of gram-negative obligate anaerobes. In addition, the combination of smoking and type 2 diabetes led to synergistic changes in the microbiome.²¹¹

3.7 | Periodontal treatment and the microbiome

Shi et al²⁰² evaluated the subgingival microbiome through metagenomic shotgun sequencing of normoglycemic and type 2 diabetes individuals with periodontitis before and after scaling and root planing. Both groups showed clinical improvement and improvements in the levels of *Prevotella intermedia*, *Po. gingivalis*, and *Ta. forsythia*. However, individuals with poor glycemic control showed a reduced shift in the microbiome; and a reduced shift towards a healthy state.²⁰² Silva-Boghossian et al²¹⁰ used a targeted approach method (ie, DNA-DNA hybridization) to evaluate 45 species, and observed similar results. Scaling and root planing led to improvement in clinical parameters and a reduction in the pathogenic bacteria in both groups, but the reduction in the type 2 diabetes group was not as significant as that observed in the normoglycemic group. Regarding the findings of Silva-Boghossian et al,²¹⁰ it is worth noting that the patients with type 2 diabetes had more severe periodontitis compared with the normoglycemic individuals. Therefore, based on the data presented above, it appears that periodontitis treatment leads to a less pathogenic bacterial profile; however, the shift is not as prominent in type 2 diabetes and is even less significant in patients with poorer glycemic control.

TABLE 4 Diabetes mellitus, periodontitis, and the microbiome

Authors	Cross-sectional or Longitudinal	Age of patients (y)	Number of patients	Diabetes parameters	Periodontitis parameters	Results
Supragingival microbiome						
Sbordone et al ³⁰²	Longitudinal (3 y)	9 to 17	32	HbA1c	PD, CAL, and BOP	There is no significant differences in clinical parameters between type 1 diabetes mellitus and non-diabetes mellitus siblings
Silva-Boghossian et al ²¹⁰	Longitudinal (3 mo)		40	FPG and HbA1c	PD and CAL, BOP, S, and marginal bleeding	After scaling and root planing, healthy individuals demonstrated improved periodontal status and reduced levels of putative periodontal pathogens at 3 mo compared with those with inadequate metabolic control
Tam et al ⁷⁷	Longitudinal (3 mo)	18 to 80	18	HbA1c	PD, CAL, BOP, and PI	Differences in microbial composition and diversity between obese and nonobese groups were statistically significant
Shi et al ²⁰²	Longitudinal (4-7 wk)		31	HbA1c	PD, CAL, BOP, and GI	In individuals with periodontitis, the shift in the subgingival microbiome from the healthy state was less prominent in type 2 diabetes compared with healthy subjects
Longo et al ²⁰¹	Cross-sectional	Adequate GC: 57.9 ± 8.39, Inadequate GC: 52.55 ± 5.32	21	HbA1c	PD, CAL, BOP, marginal bleeding	The microbiome of individuals with adequate glycemic control had higher diversity than individuals with inadequate glycemic control. Inadequate glycemic control favored fermenting species. Higher abundances of anginosus group and <i>Streptococcus agalactiae</i> in diabetes may suggest that subgingival sites can be reservoir of potentially invasive pathogens
Rodríguez-Hernández, et al ²⁰⁵	Cross-sectional	≥ 18 (non-T2DM) and ≥ 35 (T2DM)	178	HbA1c	PD, CAL, BOP, S, and gingival inflammation	The microbial profile of individuals with type 2 diabetes was different from non-type 2 individuals' microbiota
Farina et al ¹⁹⁵	Cross-sectional	≥ 40	12	HbA1c/ Med	PD and CAL	The presence of type 2 diabetes and/or periodontitis was associated with a subgingival microbiome decrease in richness and diversity. The presence of type 2 diabetes was not associated with significant differences in the relative abundance of 1 or more species in patients either with or without periodontitis
Salivary microbiome						
Sabharwal et al ¹⁹⁸	Cross-sectional	18 to 65	146	HbA1c	PD, BOP, and GI	Oral microbial diversity decreased in diabetes and increased with progression of periodontitis compared with periodontally healthy controls

(Continues)

TABLE 4 (Continued)

Authors	Cross-sectional or Longitudinal	Age of patients (y)	Number of patients	Diabetes parameters	Periodontitis parameters	Results
Yang et al ¹⁹⁶	Cross-sectional			FPG	PD, GI, recession, and mobility	Salivary microbes were related to drug treatment and certain pathologic changes
Matsha et al ¹⁹⁷	Cross-sectional	mean: 47.0 ± 13.0	128	FPG and HbA1c	PD, BOP, and CPI	Actinobacteria were significantly more abundant in subjects with diabetes, while <i>Proteobacteria</i> were less abundant. In the presence of gingival bleeding and diabetes, as compared with diabetes without gingival bleeding, Actinobacteria were markedly reduced while Bacteroidetes were more abundant. By contrast, no differences in Actinobacteria or Bacteroidetes abundance were observed between diabetes with and without PD ≥ 4 mm

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; CPI, community periodontal index; FPG, fasting plasma glucose; GI, gingival bleeding index; GC, glycemic control; HbA1c, hemoglobin A1c; Med, medication; PD, probing depth; PI, plaque index; S, suppuration; T2DM, type 2 diabetes mellitus.

3.8 | Type 2 diabetes and the salivary microbiome

Goodson et al²¹² suggested that increased levels of glucose in the saliva may affect the salivary microbiome. To test this hypothesis, several groups evaluated the role of type 2 diabetes on the salivary microbiome. Salivary and subgingival microbial diversity were decreased in individuals with type 2 diabetes.¹⁹⁸ However, treatment with metformin or metformin in combination with other medications did not rescue the flora. Nonetheless, the supragingival microbiome is different in patients with type 2 diabetes without medications and those being treated with metformin or with a combination of medications.¹⁹⁶ Another study by the same group¹⁹⁶ evaluated the salivary microbiome of normal weight, obese, and obese/type 2 diabetes children (aged 10-19 years), noting that there was minimal difference in the alpha diversity among these groups. This study supported a modest link between periodontal inflammation and type 2 diabetes in the pediatric population. The gingival index was higher in individuals with type 2 diabetes but periodontitis was similar among the groups. At the genus level, there was a difference in abundance in eight operational taxonomic units and, after adjusting for the gingival index, there were still five significantly different genus-level operational taxonomic units.²¹³ While the rate of missing, decayed, and filled teeth was similar among groups, the gingival index was higher in type 2 diabetes. There was no difference in periodontitis, which is not surprising, given that periodontitis is more common in older populations.

3.9 | Summary of type 2 diabetes, periodontitis, and the microbiome

In summary, type 2 diabetes affects the subgingival and salivary microbiome profile by decreasing diversity and richness. When glycemic control is added to the equation, there is a further decrease in diversity in individuals with inadequate glycemic control. Interestingly, the bacterial shift observed in individuals with periodontitis is less prominent in subjects with type 2 diabetes compared with normoglycemic controls. Moreover, in smokers, the diversity of the microbiome is further reduced. In future studies, it will be interesting to examine the potential for a bidirectional relationship between the periodontal microbiome and diabetes; that is, the potential for periodontal microbes to directly induce diabetes-related pathology, since evidence suggests that pathogenic microbes from the gut of obese diabetic patients can directly induce diabetes-related symptoms in rodent models.

4 | CARDIOVASCULAR DISEASE

Cardiovascular disease is a group of disorders of the heart and blood vessels that includes coronary artery disease, cerebrovascular disease, congestive heart failure, and peripheral vascular disease.^{214,215} In the USA, among individuals older than 20 years of age, 37.4% of

men and 35.9% of women have some form of cardiovascular disease.²¹⁴ These conditions can lead to myocardial infarction and stroke and they account for one third of all deaths worldwide.²¹⁶ Of these conditions, atherosclerotic cardiovascular disease is the leading cause of vascular disease worldwide.²¹⁷ Although genetics plays a role in cardiovascular disease,²¹⁸ the key risk factors stem from lifestyle, such as dyslipidemia, hypertension, tobacco smoking, and altered glucose metabolism.²¹⁹ Unfortunately, these key lifestyle factors are quite common and it is believed that 47% of Americans have at least one of them.²²⁰

Given the prevalence of cardiovascular disease and the need to prevent and treat it, Matilla et al²²¹ sought to investigate early on whether dental disease could be correlated with the prevalence of cardiovascular disease, or more specifically with myocardial infarction. The authors concluded that dental health (periapical lesions, caries, vertical bone loss, and radiolucency in the furcation) was worse in patients with acute myocardial infarction compared with healthy individuals.²²¹ In addition, significant interest has been focused on the potential role of periodontitis in cardiovascular disease. Our review of cardiovascular disease and periodontitis will be succinct, given that, in 2020, a consensus report was published on this topic by the European Federation of Periodontology and the World Heart Federation.²²²

4.1 | Periodontitis and cardiovascular disease markers

Many inflammatory and oxidative stress markers are shared by cardiovascular disease and periodontitis. Therefore, the premise that periodontitis could affect cardiovascular disease is based on the elevated inflammatory serum marker levels in patients with periodontitis compared with periodontally healthy individuals, or patients who have been treated for periodontitis.²²³⁻²²⁹

4.2 | Role of periodontitis in cardiovascular disease

Most clinical studies have shown an association between periodontitis and cardiovascular disease.²³⁰⁻²⁴¹ In 2012, a scientific statement was released by the American Heart Association confirming that there was an association between cardiovascular disease and periodontitis, but that a causal relationship could not be determined.²⁴² Around the same time, a systematic review performed by Dietrich et al²⁴³ evaluated 12 studies and also concluded that there is an association between periodontitis and atherosclerotic cardiovascular disease. However, the authors cautioned that their findings may apply only to certain populations.²⁴³ A large Swedish case-controlled study later evaluated periodontitis and its relation to coronary disease in 805 individuals and concluded that the risk of myocardial infarction significantly increases in patients with periodontitis (odds ratio: 1.28, confidence interval: 1.03-1.6), even after adjusting for variables such as smoking habits, diabetes, years of education, and

marital status.²³² A more recent study by Sen et al²⁴⁴ also concluded that patients with periodontitis have more than double the risk of cardioembolic and thrombotic stroke compared with periodontally healthy individuals. Recently, a review was performed by Herrera et al²⁴⁵ with the aim of evaluating the association between periodontitis and cardiovascular disease, to assist in the 2020 consensus report published by the European Federation of Periodontology and the World Heart Federation. The authors concluded that individuals with periodontitis have a higher prevalence of coronary artery disease and an increased risk of myocardial infarction. However, when evaluating the role of periodontitis in a secondary atherosclerotic cardiovascular disease event, there was no consensus.^{222,245}

4.3 | Effect of periodontal treatment on cardiovascular disease

Based on several observational studies and a Cochrane review that evaluated (a) self-reported toothbrushing frequency, (b) improved oral hygiene, (c) dental visit frequency, (d) periodontal treatment, and (e) periodontal treatment outcomes, and correlated them to cardiovascular events,²⁴⁶⁻²⁵² the 2020 consensus report by the World Heart Federation and the European Federation of Periodontology concluded that the progression of atherosclerotic cardiovascular disease may be influenced by successful periodontal treatment, including oral health instructions and more frequent dental visits, independent of traditional cardiovascular disease risk factor management. However, the consensus report found insufficient evidence to support or refute the potential benefit of periodontitis treatment in preventing or delaying atherosclerotic cardiovascular disease events.²²²

Interventional studies have sought to evaluate the effect of periodontal treatment on surrogate markers of cardiovascular disease, such as C-reactive protein, fibrinogen, lipid profiles, white blood cells, and blood pressure.^{236,253-257} In 2012, Bokhari et al²⁵³ evaluated patients with coronary heart disease and periodontitis and compared the effects of scaling and root planing with no periodontal treatment. The authors concluded that scaling and root planing decrease C-reactive protein, fibrinogen, and white blood cell counts.²⁵³ Caula et al²⁵⁵ evaluated patients who underwent periodontal treatment and were then followed for a period of 6 months. The authors concluded that periodontal treatment leads to a reduction in C-reactive protein, in addition to a reduction in triglycerides and erythrocyte sedimentation rates.²⁵⁵ Houcken et al²⁵⁷ recorded a decrease in systolic blood pressure after periodontal treatment. Moreover, data from a systematic review and meta-analysis concluded that periodontal treatment, in addition to reducing serum levels of atherosclerotic cardiovascular disease biomarkers, improves endothelial function.²⁵⁸

To assess whether the timing of periodontal treatment has systemic effects, Graziani et al²⁵⁶ compared scaling and root planing performed within 24 hours vs scaling and root planing performed over a 4-week period and evaluated inflammatory markers. The

results indicated that there is an increased acute phase response, demonstrated by increased C-reactive protein and interleukin-6, when full mouth scaling and root planing are performed in a 24-hour period. However, these results were transient and both treatment modalities ultimately offered similar results. Nonetheless, further studies are needed to determine if the elevated acute phase response has any impact on cardiovascular disease risk.²⁵⁶

The data presented here are in agreement with the 2020 World Heart Federation and European Federation of Periodontology consensus report, which points to evidence that periodontal treatment may reduce low-grade systemic inflammation.²²² It is important to note that a review by Herrera et al²⁴⁵ also pointed out that there have been a limited number of studies evaluating the role of periodontal treatment on cardiovascular disease outcomes.

4.4 | Periodontal microbiome and cardiovascular disease

Considerable attention has been given recently to the microbiome because of its ability to modulate chronic conditions, including cardiovascular disease.^{259,260} Given that periodontitis is triggered by a dysbiosis of pathogenic bacteria, that certain dental procedures, including toothbrushing, scaling, and root planing cause a transient bacteremia, and that periodontitis has been correlated with cardiovascular disease,²⁶¹⁻²⁶⁷ researchers sought to determine if periodontopathogens could be found in the cardiovascular system. Indeed, several groups have identified periodontal pathogens, such as *Tr. denticola*, *Aggregatibacter actinomycetemcomitans*, *Po. gingivalis*, and *Ta. forsythia*, in cardiovascular tissue specimens (including atherosclerotic plaque, aortic valve, mitral valve, and aortic aneurysm).²⁶⁸⁻²⁷² Although the mechanism by which bacteria enter into circulation is not fully understood, one study suggests that dendritic cells phagocytose and disseminate surviving periodontopathogens to atherosclerotic plaques and that these "primed" dendritic cells may provide key signals for atherogenic conversion.²⁷³

Moreover, while most studies were able to identify pathogenic periodontal bacteria in cardiovascular tissues, the exact role of the bacteria in cardiovascular disease is not fully understood. In an in vitro study, Lonn et al²⁷⁴ suggested that *Po. gingivalis* can modify vascular low-density lipoprotein, very low-density lipoprotein, and high-density lipoprotein to an atherogenic form. A clinical study suggested that microRNA-146, a regulator of innate immune responses, was a key molecule in associating periodontitis with coronary artery syndrome because of its dysregulation by periodontal pathogens.^{275,276} Moreover, a review by Reyes et al²⁷⁷ effectively categorized the available research indicating that periodontal bacteria (a) disseminate and reach systemic vascular tissue, (b) are found in the affected tissues, (c) live within the affected site, (d) invade affected cell types in vitro, and (e) induce atherosclerosis in animal models of disease; (f) correct that noninvasive mutants of periodontal bacteria cause

significantly reduced pathology in vitro and in vivo, and (g) that periodontal isolates from human atheromas can cause disease in animal models of infection.

To summarize the human and animal studies regarding the role of periodontal bacteria in cardiovascular disease, there are convincing data showing that periodontal bacteria can be found in cardiovascular tissues, but the role that bacteria play in these tissues still needs to be further elucidated.

4.5 | The role of cardiovascular disease in periodontitis

While much emphasis has been placed on determining the potential role of periodontitis in cardiovascular disease, little has been done to evaluate the role of cardiovascular disease in periodontitis. As a result, the European Federation of Periodontology and World Heart Federation consensus report concluded that, to date, there is little scientific evidence that cardiovascular disease is a risk factor for periodontitis.²²²

In conclusion, much is known about the role of periodontitis in cardiovascular disease. However, it is important to note that these two conditions share risk factors, such as smoking, age, socioeconomic conditions, and obesity, which may lead to a possible common pathophysiology for periodontitis and cardiovascular disease.²⁷⁸⁻²⁸⁰

4.6 | Lessons from animal models: periodontitis and cardiovascular disease

In addition to the role of periodontal bacteria in cardiovascular disease, as discussed above, animal studies have shed some light on the role of periodontitis in cardiovascular disease. Animal models have demonstrated that periodontitis increases systemic inflammation and that cardiovascular disease markers, such as C-reactive protein, interleukin-1-beta, interleukin-6, and vascular superoxide production, worsen lipid profile levels (total cholesterol, low-density lipoprotein, and triglycerides).²⁸¹⁻²⁸³ Evaluating endothelial changes in a ligature-induced periodontitis model in rats, Brito et al²⁸³ observed a reduction in endothelium-dependent vasodilatation, which is the hallmark of endothelial dysfunction. Moreover, Kose et al²⁸¹ performed histologic analysis of the left ventricular heart tissues of rats and demonstrated that, at an early stage, periodontitis causes degenerative and hypertrophic changes in the heart tissue, and that prolonged systemic inflammatory stress caused by periodontitis may enhance the risk of hypertrophic changes.

In attempting to understand the role of periodontitis in cardiovascular disease, most studies have focused on the role of periodontopathogens in atherosclerosis because of their ability to induce severe oxidative stress, induce an inflammatory response, invade, colonize, and escape immune detection.²⁸⁴⁻²⁸⁷ For instance, in response to *Po. gingivalis*, endothelial cells undergo

oxidative stress and secrete various cytokines, such as tumor necrosis factor- α , interleukin-1- β , interleukin-6, and interferon gamma.^{285,288} Part of the mechanism by which *Po. gingivalis* accelerates atherosclerosis involves the nuclear factor kappa light chain enhancer of activated B cells signaling loop.^{289,290} Moreover, periodontal pathogens are able to modulate lipid influx via fatty acid binding protein 4 in macrophages, strongly supporting another mechanism by which periodontitis may affect atherosclerotic progression.²⁹¹

5 | CONCLUSIONS

Metabolic syndrome, diabetes, and cardiovascular diseases are associated with periodontitis. Moreover, there is evidence to suggest that metabolic syndrome and diabetes can alter the oral microbiome. However, more studies are needed to fully understand the influence these conditions have on each other.

6 | METHODS

This study was approved by the Institutional Review Board of the University of Michigan Medical School (#HUM000068346.) Twenty-two subjects older than 18 years of age with a minimum of 10 teeth were recruited, and informed consent was obtained. Pregnant and lactating women were excluded from the study.

6.1 | Subject diagnoses

A single examiner collected clinical data including the subjects' weight, height, waist and hip circumference, blood pressure, and blood glucose levels. Subjects were diagnosed as healthy or metabolic syndrome. A diagnosis of metabolic syndrome was given to subjects who exhibited three or more of the following parameters: abdominal obesity (waist circumference of > 102 cm in men or > 88 cm in women), hyperlipidemia (self-reported), hypertension (> 120 diastolic or > 80 systolic readings or use of antihypertensive medication), or diabetes (self-reported or elevated blood glucose > 120 mg/dl).²⁹² Patients who did not meet these criteria were considered systemically healthy and were assigned to the healthy group rather than the metabolic syndrome group.

Periodontal screening and recording examinations were completed for each subject. Subjects with no evident signs of gingivitis or periodontitis, who had probing depths of 1-3 mm, bleeding on probing less than 30%, and no evidence of radiographic bone loss, were diagnosed as healthy periodontium. Subjects were diagnosed with periodontitis if they displayed severe gingival inflammation, erythema, possible edema, bleeding on probing greater than 30%, radiographic bone loss greater than 15%, and probing depths greater than 5 mm in more than one quadrant.

6.2 | Data analysis

6.2.1 | Two-group analysis: healthy vs metabolic syndrome

A two-group analysis was completed as follows: healthy subjects were compared with subjects with metabolic syndrome. The metabolic syndrome group included those with a healthy periodontium as well as those with periodontitis. The 12 metabolic syndrome patients had diabetes mellitus. No tobacco smokers were included in the healthy group, but of the metabolic syndrome population, five were current smokers and three were former smokers. Healthy subjects were aged 20-46 (mean 28.1) years while metabolic syndrome subjects were aged 47-78 (mean 64.5) years.

6.2.2 | Four-group analysis: healthy vs healthy* vs metabolic syndrome healthy periodontium vs metabolic syndrome periodontitis

A four-group analysis was conducted on the following groups: (1) healthy (medically and dentally), (2) healthy* (subjects who presented with elevated blood pressure readings despite the subject having no self-reported history of hypertension), (3) metabolic syndrome with healthy periodontium (metabolic syndrome healthy periodontium), and (4) metabolic syndrome with periodontitis (metabolic syndrome periodontitis). The healthy group consisted of seven subjects. Three healthy subjects presented with an elevated systolic and/or diastolic blood pressure reading (stage I hypertension values, according to the American Heart Association) and thus were stratified into a healthy* group. When questioned, all three subjects confirmed that they sought regular, routine medical care with a physician and had not been diagnosed as prehypertensive or hypertensive. Metabolic syndrome subjects were stratified into two groups, four metabolic syndrome healthy periodontium and eight metabolic syndrome periodontitis. Of the metabolic syndrome periodontitis group, seven (out of eight) subjects had a history of tobacco use (six current smokers and one former smoker), whereas the metabolic syndrome healthy periodontium group had only one former tobacco user.

6.3 | Salivary analysis

Passive saliva was collected from each subject for 5 minutes. Samples were subsequently stored in a -80°C freezer until they were prepared for analysis. Prior to analysis, samples were thawed and centrifuged. Whole genomic bacterial DNA was extracted from salivary pellets and purified using MasterPure DNA purification kit (Epicentre, Madison, WI, USA). DNA was adjusted to a concentration of 20 ng/ μl using a NanoDrop (Thermo Fisher Scientific, Waltham, MA, USA).

The 16S rDNA next generation sequencing was performed using the Human Oral Microbiome Identification system (The Forsyth

Institute, Cambridge, MA, USA).^{293,294} The laboratory procedures of the Human Oral Microbiome Identification system follow a method modified from a previously published protocol.²⁹⁵ PCR amplification of DNA (10–50 ng) was performed using universal primers targeting the V3–V4 region of 16S genes (F341, R806). The products were purified using AMPure purification. Amplicons were pooled in libraries (100 ng) that were gel-purified and quantified by quantitative PCR before being sequenced (MiSeq, Illumina, San Diego, CA, USA). In this study, reads were typically more than 50 000 per sample. The sequence read pairs were merged to single reads with a script (*join_paired_ends.py*) provided by quantitative insights into microbial ecology package version 1.91 with default settings. The merged reads were then taxonomically assigned to the species level based on a published algorithm²⁹⁶ with additional steps to further identify potential novel species. A complete description and the results of the taxonomy assignment are available online at http://www.homd.org/ftp/publication_data/20170412/. Basic local alignment search tool nucleotide was used to compare merged sequence reads with a panel of full-length 16S ribosomal RNA sequences, consisting of 889 sequences from human oral microbiome database reference sequence V14.5, 495 from human oral microbiome database reference sequence extended V1.1, 3940 from GreenGeneGold, and 18 166 from the National Center for Biotechnology Information 16S rRNA reference. This combined reference set has a total of 23 490 sequences and represents 13 640 oral and non-oral microbial species. After the taxonomy assignment, species-level operational taxonomic units with at least 10 reads were subjected to several downstream bioinformatic analyses, including alpha and beta diversity assessments, provided in quantitative insights into microbial ecology. Samples with less than 500 read counts were excluded from the quantitative insights into microbial ecology analysis. Species-level taxonomic plots were generated. Alpha and beta diversity measures were calculated for two- and four-group analysis. Alpha diversity and species richness were evaluated with rarefaction plots using the operational taxonomic units as the metric. Beta diversity was evaluated with principal coordinate analysis plots, created using generalized UniFrac as the distance measurement based upon the R statistic generated using analysis of similarities.

Additionally, quantitative insights into microbial ecology data were used to employ galaxy for linear discriminant analysis effect size for metagenomic analysis. A histogram was generated to visualize the effect size (linear discriminant analysis) difference for two- and four-group analysis. A cladogram taxonomic tree was generated to evaluate the phylogenetic comparisons for the two- and four-group analyses at the species level.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed by the current study are available online at http://www.homd.org/ftp/publication_data/20170412/qiime_results/cd_mc10/taxa_plots/taxa_summary_plots/bar_charts.html.

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