Chronic Periodontitis with Multiple Risk Factor Syndrome: A Case Report

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Abstract

Objective: Multiple risk factor syndrome is a clustering of cardiovascular risk factors, such as diabetes, dyslipidemia, hypertension, and obesity associated epidemiologically with insulin resistance. This report describes the clinical course of a patient suffering from severe periodontitis with multiple risk factor syndrome, and discusses the association between periodontal infection and systemic health. **Methods:** The patient had a history of type 2 diabetes, dyslipidemia, and hypertension for over 10 years. At baseline, her hemoglobin A1c was 8.1%. However, she had no diabetic complications except periodontitis. The IgG antibody titers against *Porphyromonas gingivalis* FDC 381 and SU63 were elevated above the mean of healthy subjects +2 standard deviations. Intensive periodontal treatment, including periodontal surgery, was performed to reduce periodontal infection and bacteremia. Her systemic and periodontal conditions were evaluated longitudinally for 10 years. **Results:** Following periodontal treatment, antibody titers against *Porphyromonas gingivalis* and hemoglobin A1c values were significantly improved. The other clinical data and medication for her systemic condition also remained stable during supportive periodontal therapy. However, she developed myocardial infarction, and showed continuous deterioration of hemoglobin A1c level and periodontitis. **Conclusion:** The long-term clustering of risk factors, such as diabetes, dyslipidemia, hypertension, and periodontitis, are associated with the development of myocardial infarction. Treatment of systemic conditions in combination with comprehensive periodontal treatment is important in management of patients with multiple risk factor syndrome.

Keywords: Periodontitis, type 2 diabetes mellitus, cardiovascular disease, multiple risk factor clustering syndrome, case report

Introduction

Periodontal disease is the sixth most common complication of diabetes mellitus because diabetes patients often have an increased prevalence of periodontal disease (Loe, 1993). Periodontal disease may also affect blood glucose levels in diabetic patients through insulin resistance. There has been a recent focus on understanding the negative influences of oral chronic inflammation on systemic health (Mealey and Oates, 2006; Nishimura *et al.*, 2007; Genco and Van Dyke, 2010).

Cardiovascular disease complicated with diabetes mellitus is the primary cause of death in diabetic patients (Haffner *et al.*, 1998). The Hisayama study in Japan (Fujishima *et al.*, 1996) indicated that the incidence of cardiovascular disease was three times higher in subjects with type 2 diabetes than in those with normal glucose tolerance. A recent epidemiological study indicated that an increase of 1% in the hemoglobin A1c (HbA1c) level is associated with an 18% increase in the risk of cardiovascular events

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(Selvin *et al.*, 2004). The incidence rate of cardiovascular disease is influenced by impaired insulin resistance complicated with diabetes, hypertension, dyslipidemia, and obesity (Fujioka *et al.*, 1987; Reaven, 1988; Kaplan, 1989; DeFronzo and Ferrannini, 1991). Taken together, these systemic diseases are defined as multiple risk factor syndrome (MRFS), a clustering of cardiovascular risk factors associated with insulin resistance. Furthermore, previous studies have indicated a strong correlation between cardiovascular disease and periodontitis, and it has also been suggested that persistent subclinical infection in periodontitis may influence susceptibility to cardiovascular disease as an independent risk factor (Beck *et al.*, 1999; Wu *et al.*, 2000). Other epidemiological studies have also shown that periodontal infection is significantly associated with subclinical and clinical cardiovascular disease (Taniguchi *et al.*, 2003; Desvarieux *et al.*, 2005; Dietrich *et al.*, 2008). Therefore, in clinical cases, patients suffering from severe periodontitis with MRFS are considered at high risk for atherosclerosis, such as ischemic heart disease. Accumulating clinical data from diverse cases and characterization of each risk factor is important to prevent subclinical infection-associated cardiovascular disease.

Here, we describe the long-term clinical course of a female patient suffering both severe periodontitis and MRFS. Her blood glucose control was significantly improved following periodontal treatment, but she developed myocardial infarction and stroke, and then heart failure during the supportive periodontal therapy (SPT) phase. We discuss the pathogenesis of cardiovascular disease influenced by MRFS and periodontitis, with emphasis on the relevance of glycemic control.

Case report

A 62-year-old Japanese woman was referred to the Okayama University Hospital, Department of Periodontics and Endodontics for treatment of severe periodontitis characterized by gingival pain and swelling for the past two years. Her physician recommended that she should visit a specialist to examine the association between diabetes mellitus and periodontitis. The subject provided informed consent before entry into this study.

Systemic condition

The patient had been diagnosed with type 2 diabetes for 10 years, dyslipidemia for 9 years, and hypertension for 8 years. She was treated with insulin injection (12 units per day) for diabetes, and was taking medication for dyslipidemia (reductase antagonist) and hypertension (calcium antagonist). Her HbA1c value was 8.1%, blood pressure was 145/90 mmHg, total cholesterol was 230 mg/dL, and body mass index (BMI) was 21.3 kg/m2. She had no diabetic complications and no history of smoking. All medications for her systemic conditions had remained stable during the last two years, since 1998.

Clinical oral examination

Oral examination revealed moderate redness and swelling in the interproximal gingival papilla (*Figure 1*). The maxillary anterior teeth were flared out, and the patient had loss of several teeth with no prosthodontic treatment. Plaque control record (PCR) (O'Leary *et al.*, 1972) was 60%. Probing pocket depth $\geqslant$ 4 mm was 68%, and the ratio of bleeding on probing (BOP) was 80% *(Table 1)*. Teeth with severe bone loss showed mobility ranging from 2 to 3 (Lindhe and Nyman, 1987). Radiographic examination revealed moderate horizontal alveolar bone loss, calculus, and localized areas of severe vertical alveolar bone loss (teeth 5, 12, 13, 22, and 23, *Figure 2*).

Detection of periodontal infection

The humoral immune responses to 12 periodontal bacteria were assayed by enzyme-linked immunosorbent assay (ELISA) as described previously (Murayama *et al.*, 1988). The serum IgG antibody titers against *Porphyromonas gingivalis* (Pg) FDC 381 and Pg SU63 were elevated over the mean of healthy subjects' +2 standard deviations (A in *Figure 3*). Other serum IgG antibody titers were within normal ranges.

Diagnosis

Based on the clinical findings and humoral immune response to periodontal bacteria, a diagnosis of acute gingival abscess in teeth 5, 12, and 13, and severe generalized chronic periodontitis closely associated with Pg infection and occlusal trauma was made. In addition, uncontrolled type 2 diabetes with high blood glucose may result in exacerbation of periodontal inflammation.

Treatment

The treatment plan for this patient was to reduce periodontal infection and reduce the bacteremia, which may have affected the diabetic condition. The clinical laboratory data, including IgG antibody titers against Pg FDC 381 and Pg SU63, were assessed periodically. After medication with cephem antibiotics to relieve acute inflammation, her oral hygiene was improved (PCR 26%) by tooth-brushing instruction. Subgingival scaling and root planing were performed combined with application of 2% minocycline slow-release ointment (Iwamoto *et al.*, 2001) once a week for four weeks. A temporary prosthesis was applied to reduce the occlusal trauma. Hopeless teeth (5, 12, and 13) were extracted, and periodontal surgery was performed (flap operation and labial frenectomy on the upper lip) with premedication using cephem antibiotics.

Table 1. Clinical findings at baseline and SPT

	Baseline	SPT
No. of teeth	23	20
Mean probing depth (%)*		
< 4 mm	32	99
⩾ 4 mm, < 6 mm	58	1
⩾ 6 mm	10	0
Bleeding on probing (%)	80	3

*Percent of sites with indicated probing depth. Baseline, first visit (August 2000); SPT, start of supportive periodontal therapy phase (February 2002).

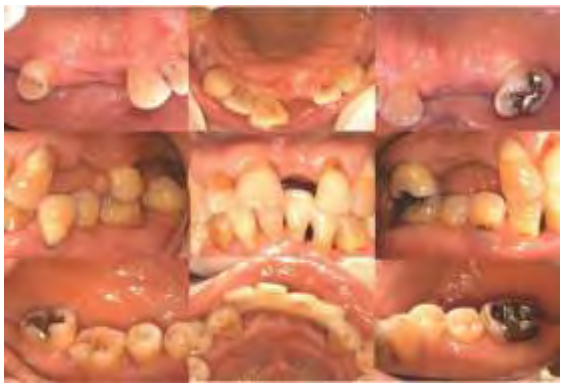

Figure 1. Oral photographs at baseline: Slight to moderate gingival inflammation was observed. Hard and fibrotic swelling was noted in the lower anterior gingiva, which may be attributable to an effect of a calcium antagonist. Teeth 5, 12, and 13 had already been extracted.

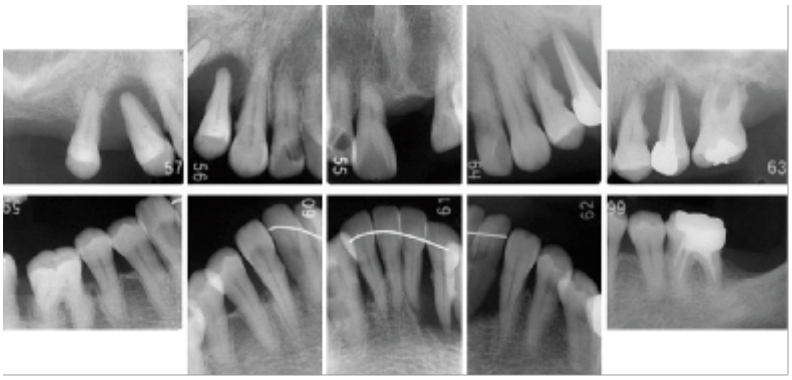

Figure 2. Dental radiographs at baseline: Generalized horizontal alveolar bone loss was observed. Extreme bone loss was prominent at the upper premolar with a "floating teeth" appearance. Advanced bone loss was also observed at the lower left incisor.

Supportive periodontal therapy

After surgery and prosthodontic treatment, the patient was placed on a supportive periodontal therapy (SPT) program once a month. Gingival inflammation was resolved *(Figure 4)*, and all sites had probing pocket depths ⩽ 3 mm except tooth 19 *(Table 1)*. Radiographic examination revealed obvious lamina dura in the alveolar bone *(Figure 5)*. The patient was motivated to maintain daily plaque control (average PCR 15%), and her systemic and oral condition were good for the first 2 years 5 months since commencement of SPT. However, she discontinued recall appointments as she developed myocardial infarction, stroke (3 years 11

months from baseline), and heart failure (5 years 3 months from baseline). Finally, at 5 years 6 months from baseline (1 year 7 months of discontinuation), she returned for treatment of gingival abscess in the mandibular left molar region. Severe gingival inflammation and swelling were observed around the distal root of tooth 19, and probing revealed a pocket depth greater than 7 mm. Subgingival debridement was performed with premedication using cephem antibiotics. Since then, no incipient bone loss and no periodontal attachment loss have been observed, and her condition has remained good.

Alterations in humoral immune response to periodontal bacteria

The IgG titers against Pg FDC 381 and Pg SU63 were markedly decreased following periodontal treatment (B in *Figure 3*), and then remained within the normal range during SPT (C in *Figure 3*). However, they were slightly elevated again when she returned for treatment after a period of discontinuation (D in *Figure 3*). The alterations of IgG titers were synchronized with the clinical data: deep pocket rate, BOP, and HbA1c level.

Changes in systemic condition

The baseline HbA1c (8.1%) was decreased to 7.0% after periodontal surgery (B in *Figure 3* and *Figure 6*). Self-monitoring of blood glucose (SMBG) was performed to prevent hypoglycemia, and also confirmed that the HbA1c value ranged from 5.7% to 6.9% during SPT (*Fig. 6*). The medication for her systemic condition, including insulin dose, remained stable for 3 years 11 months from baseline. Her blood pressure, total cholesterol, and BMI also remained within normal range from baseline. However, she was admitted with ischemic heart disease to undergo coronary arterial bypass grafting (D in *Figure 6*). During the lapse of SPT, her HbA1c value increased to 8.1% (E in *Figure 6*). After coronary surgery and periodontal treatment, the HbA1c value remained stable between 6.4% and 6.8%. During hospitalization, all medications were changed adequately to control ischemic heart disease.

Currently, the patient is receiving regular SPT with strict management of blood glucose, blood pressure, and lipid levels. After she re-entered the SPT program, all medications were stable at the basal amount. The clinical data show that the HbA1c value has decreased to 6.8%, but the level of brain natriuretic peptide (BNP), a marker of heart failure (Troughton *et al.*, 2000), is still high (280 pg/mL), and total cholesterol has remained 211 ± 16.0 mg/dL from baseline through SPT. Meanwhile, her blood pressure and BMI remained within normal range during the observation period.

Discussion

Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity and psychosocial factors account for most of the risk of myocardial infarction worldwide (Yusuf *et al.*, 2004). It is also recognized that the risk factors cluster and interact multiplicatively to promote vascular risk (Jackson *et al.*, 2005). When patients with type 2 diabetes concomitantly exhibit other features of the clustering risks, they are at particularly high risk for cardiovascular disease. In fact, the recurrence rate of major atherosclerotic complications in type 2 diabetic patients with a prior cardiovascular event is very high, around 6% per year (Giorda *et al.*, 2008). These results suggest a significant pathophysiological link between these two diseases. Furthermore, a recent epidemiological study found that MRFS is associated with an increased rate of myocardial infarction (OR: 2.69); they additionally found that clustering factors with subthreshold values are also significantly associated with an increased the risk (OR: 1.50) (Mente *et al.*, 2010). In this case, the patient's clinical data showed that blood pressure, total cholesterol, and BMI were within normal range; however, they were relatively high values. Moreover, the level of BNP, a marker of heart failure, was extremely high. These facts explain why the patient has been at high risk for cardiovascular disease during the observation period.

The patient developed a series of cardiovascular events, although her diabetic condition remained stable during SPT. There is still controversy regarding the effects of glucose control on cardiovascular events in patients with diabetes. Recent studies have indicated that intensive blood glucose control does not significantly reduce major cardiovascular events (Gerstein *et al.*, 2008; Patel *et al.*, 2008; Duckworth *et al.*, 2009). Because MRFS is chronic and multifactorial in origin, it is unlikely to be reversed by removing a single etiologic component (Jackson *et al.*, 2005). Strategies for reducing cardiovascular risk involve the management of multiple risks. It is generally accepted that not only blood glucose control but also other factors associated with coronary artery disease should be managed over the long term (Baigent *et al.*, 2005; Turnbull *et al.*, 2005; Gaede *et al.*, 2008). The patient reported here had been suffering type 2 diabetes, hypertension, and dyslipidemia for a long period prior to intensive periodontal treatment. Although blood glucose was significantly improved following the periodontal treatment, the other causative factors were present for decades prior to clinical onset. These findings suggest that the long-term clustering of these risk factors may have led to irreversible coronary lesion, and triggered a series of cardiovascular events.

Current evidence supports a central role for inflammation in all phases of the atherosclerotic process, including plaque instability, and low-grade chronic systemic inflammation has been shown to adverse affect cardiovascular outcomes (Libby *et al.*, 2002). Systemic chronic inflammation is associated with insulin resistance and diabetes, all of which are

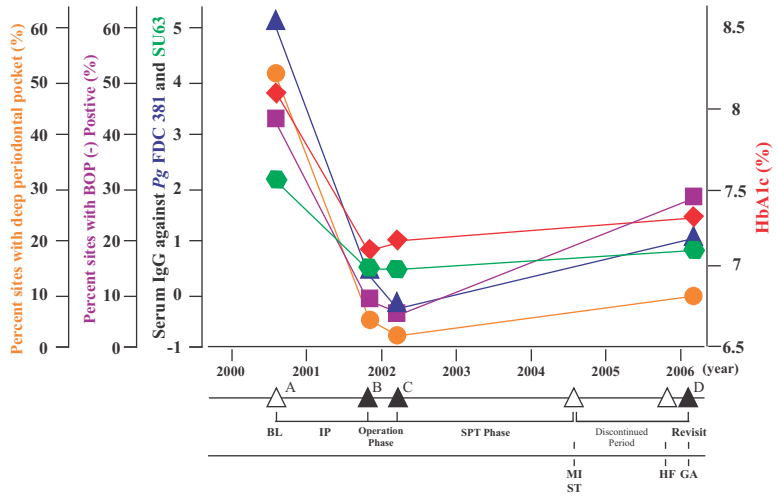

Figure 3. Improvement of clinical data during periodontal treatment: Changes in IgG titers against Pg FDC 381 and Pg SU63 were synchronized with the changes in HbA1c level and the percent sites with deep periodontal pockets and BOP. The horizontal axis represents the time course from baseline, and the vertical axis represents the clinical data. Orange circles: percent sites with deep periodontal pockets (⩾ 4 mm); violet squares: BOP rate; blue triangles: serum IgG titer against Pg FDC 381; green hexagons: serum IgG titer against Pg SU63; red diamonds: HbA1c level. A: At baseline (BL) in August 2000. B: After periodontal surgery in November 2001 (1 year 3 months from BL). C: Start of SPT phase in February 2002 (1 year 6 months from BL). D: At the time of gingival abscess (GA) in February 2006 (5 years 6 months from BL). BOP, bleeding on probing; HF, heart failure; IP, initial preparation; MI, myocardial infarction; SPT, supportive periodontal therapy; ST, stroke

features of MRFS (Hotamisligil, 2006). Therefore, periodontal infection and inflammation-associated factors have attracted attention in addition to traditional risk factors (King, 2008). Recent studies have suggested that periodontal treatments can reduce levels of clinical markers for cardiovascular disease and improve endothelial function (D'Aiuto F *et al.*, 2006; Tonetti *et al.*, 2007; Offenbacher *et al.*, 2009; Piconi *et al.*, 2009), suggesting that inflammatory cytokines induced by periodontitis could mediate the link with cardiovascular disease. However, there are no data available to date suggesting that the prevention or amelioration of periodontal infections will result in reduced incidence of cardiovascular events (Kebschull *et al.*, 2010). It has been reported that elevated values of circulating inflammatory markers may reflect not only a high prevalence of cardiovascular disease but also a primary inflammatory instigator of coronary instability (Libby *et al.*, 2002). In this case, although the intensive periodontal treatment successfully reduced periodontal infection and inflammation, there could have already been atherogenesis present at the time of treatment initiation. Further studies are required to determine the cause and effect relationship between these two diseases.

Meanwhile, a recent study demonstrated that invasive dental treatment may be associated with a transient increase in the risk of cardiovascular disease (Minassian *et al.*, 2010). Periodontal treatment can definitely cause transient bacteremia. Periodontal bacteria have been identified in atheromas and could provide the inflammatory stimulus leading to atheroma formation (Iwai, 2009). Although antibiotics have an impact on bacteremia, the efficacy of antibiotic prophylaxis is not 100% even if administered correctly (Brennan *et al.*, 2007). Periodontists should consider carefully how to reduce periodontal infection and to reduce bacteremia for cardiovascular disease prevention strategies. Another epidemiological study demonstrated that intensive periodontal treatment resulted in acute, short-term systemic inflammation and endothelial dysfunction. However, six months after therapy the endothelial function was improved (Tonetti *et al.*, 2007). Thus, the absolute risks could be estimated minimum, and the long-term benefits on vascular health will probably outweigh the short-term adverse effects.

Much evidence indicates a bidirectional relationship between diabetes and periodontal disease (Mealey and Oates, 2006; Nishimura *et al.*, 2007). Periodontitis could at least in part be related to induction of insulin resistance (Benguigui *et al.*, 2010). In the present case, the time course analysis over a 10-year observation period indicated that her HbA1c level was markedly

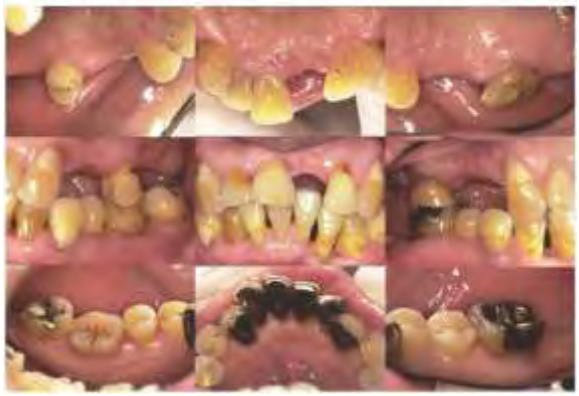

Figure 4. Oral photographs during supportive periodontal therapy: Gingival redness and swelling had disappeared. A prosthetic denture was applied to replace the upper missing teeth.

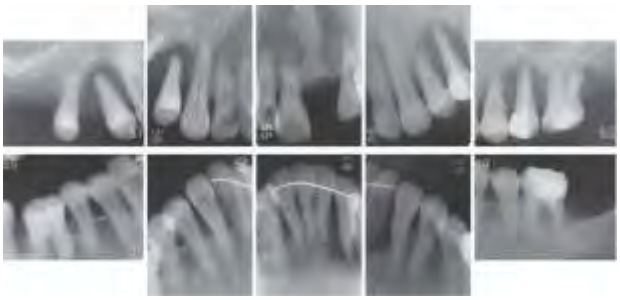

Figure 5. Dental radiographs during supportive periodontal therapy: Obvious crestal lamina dura was noted at the interproximal sites in the alveolar bone. No incipient bone loss was observed.

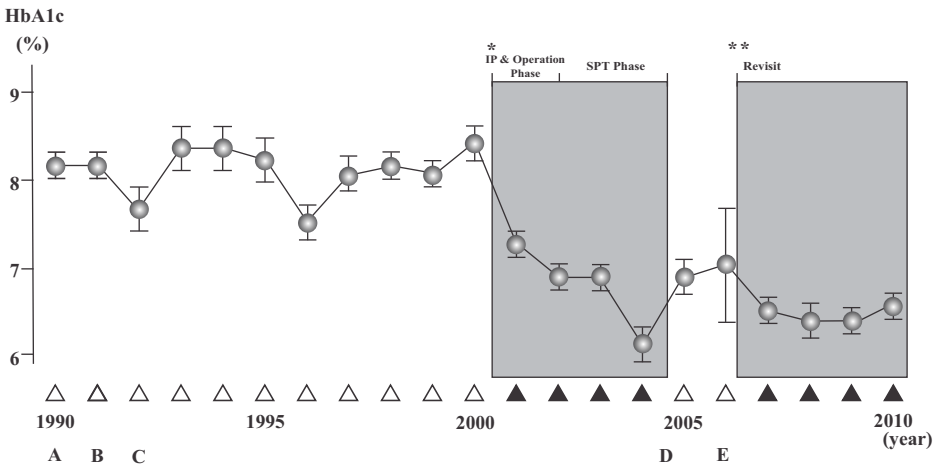

Figure 6. Alterations of HbA1c levels: The horizontal axis represents the time course and the vertical axis represents HbA1c level (%). Points indicate means ± SD of the value in each month. The gray area shows the period of regular visits to Okayama University Hospital. Insulin had been prescribed since diagnosis of type 2 diabetes. The dose of insulin remained stable from 1998 to July 2004 (D). A: Incidence of diabetes in 1990. B: Incidence of dyslipidemia in 1991. C: Incidence of hypertension in 1992. D: Incidence of myocardial infarction and stroke in 2004. E: Incidence of heart failure in 2005. *Baseline; **Incidence of gingival abscess; IP, initial preparation.

improved from 8.1% to 5.7% after periodontal treatment *(Figures 3, 6)*. The improvement of HbA1c level may have been due to the improvement of insulin resistance following reduction of circulating levels of several proinflammatory cytokines (Mealey and Oates, 2006; Nishimura *et al.*, 2007), which is probably associated with the effect of periodontal treatment. In fact, diabetic treatment and her blood pressure, total cholesterol, and BMI have remained stable since baseline.

Interestingly, deterioration of the HbA1c level was coincident with the development of cardiovascular events *(Figure 6)*. The deterioration of her systemic condition, including high blood glucose, the lifestyle change during hospitalization, and also the lapse of SPT may have affected periodontal inflammation, involving increased serum IgG titers against Pg and resulting in gingival abscess *(Figure 3)*. The precise mechanism of the unexpected increase in HbA1c level is still unclear. Atherothrombosis is characterized as more than a disease of lipid accumulation, but rather as a disorder with vascular inflammation (Ross, 1999; Libby *et al.*, 2002). The increased and prolonged release of lipids, fatty acids, and various inflammatory cytokines may be linked to the development of insulin resistance, resulting in abnormal elevation of the HbA1c level (Shoelson *et al.*, 2006).

The long-term morbidity of impaired insulin resistance adds to traditional risk factors for cardiovascular disease, such as diabetes, hypertension, and dyslipidemia. Systemic chronic inflammation is also associated with insulin resistance and contributes to cardiovascular outcomes, including the earliest steps in atherogenesis. Thus, high priority should be given to control inflammatory mediators and markers for primary and secondary prevention of cardiovascular disease. Although future research is required to evaluate risk reduction with the treatment of periodontal disease, periodontists and physicians managing patients with MRFS should closely collaborate to optimize cardiovascular risk reduction and periodontal care.

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