Editors' Consensus Report

The American Journal of Cardiology and *Journal of Periodontology* Editors' Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease♦

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The organization of the health professions into specialties and subspecialties according to body organs and systems is often more pragmatic than scientific. The human organism is a single unit composed of a seemingly infinite number of biologic processes so intertwined that abnormalities of almost any of its parts or processes have profound effects on multiple other body areas, exemplified in this document by the common and complex theme of *inflammation*. In recent years, the immune system, once believed to be only a vital defense against infection and a promoter of healing—except in the instances of a few uncommon connective tissue disorders—is now recognized as a significant active participant in many chronic diseases, including hypertension, diabetes mellitus, arthritis, inflammatory bowel disease, psoriasis, and the two diseases addressed in this Editors' Consensus: atherosclerotic cardiovascular disease (CVD) and periodontitis.

This aim of this document is to provide health professionals, especially cardiologists and periodontists, a better understanding of the link between atherosclerotic CVD and periodontitis and, on the basis of current information, an approach to reducing the risk

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for primary and secondary atherosclerotic CVD events in patients with periodontitis.

Periodontitis, a bacterially induced, localized, chronic inflammatory disease, destroys connective tissue and bone that support the teeth. Periodontitis is common, with mild to moderate forms affecting 30% to 50% of adults and the severe generalized form affecting 5% to 15% of all adults in the United States.[1] Periodontitis has even higher prevalence in developing countries and considerable global variation, although the prevalence of the severe generalized disease appears to be similar in most populations.[2]

Patients with periodontitis are often asymptomatic. When present, physical signs and symptoms are nonspecific and include (Fig. 1) swollen gums that decompress, discolored gums, tender gums, bleeding gums (spontaneous or after brushing or flossing), long appearance of teeth (because of receded gums), increased spacing between teeth, pus between teeth and gums, loose teeth, change in tooth sensation when biting because of increased tooth mobility, bad taste, and halitosis (because of anaerobic infection). Patients with periodontitis who have spontaneous oral pain or pain on mastication often have complications of the disease, including abscesses and other oral mucosal and alveolar bone lesions.

The clinical diagnosis of periodontitis requires evaluation by a trained examiner and evidence of gingival inflammation, loss of connective tissue surrounding the teeth measured by clinical examination using a periodontal probe, and bone loss detected by radiography (Fig. 2).

Although moderate to severe periodontitis may affect systemic inflammatory and immune markers (e.g., elevated blood levels of C-reactive protein [CRP]), such changes are either not captured by current standard laboratory test panels or are interpreted as nonspecific indicators of a chronic, low-grade, acute-phase inflammatory response. Patients with uncomplicated periodontitis have no systemic signs of infection, such as fever or leukocytosis.

Pathophysiology

Periodontitis begins with a microbial infection, followed by a host-mediated destruction of soft tissue caused by hyperactivated or primed leukocytes and the generation of cytokines, eicosanoids, and matrix metalloproteinases that cause clinically significant connective tissue and bone destruction.[3] Bacterial accumulations on the teeth are essential to the initiation and progression of periodontitis. Cells that mediate immunity, such as neutrophils, play a major role in the host response against invading periodontopathogenic microorganisms. When bacterial biofilms on the teeth are not disrupted on a regular basis, ecologic changes lead to the emergence of a small set of gram-negative anaerobic

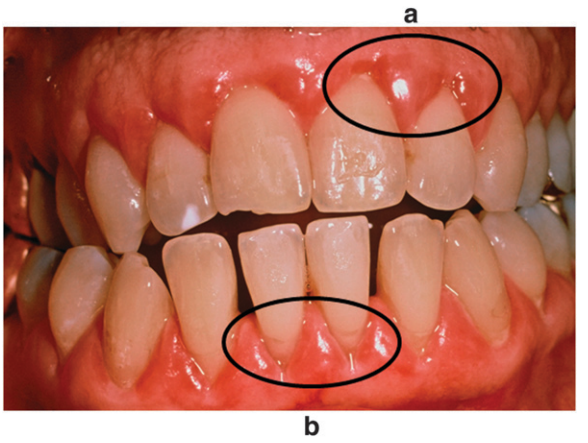

Figure 1.
In this patient with mild to moderate periodontitis, changes in tissue contours and color are present (a). Root surfaces that have been exposed with gingival recession due to destruction of the connective tissue attachment (b) may appear light gray to yellow in color. Spaces between the mandibular teeth are usually a sign of drifting due to loss of supporting bone.

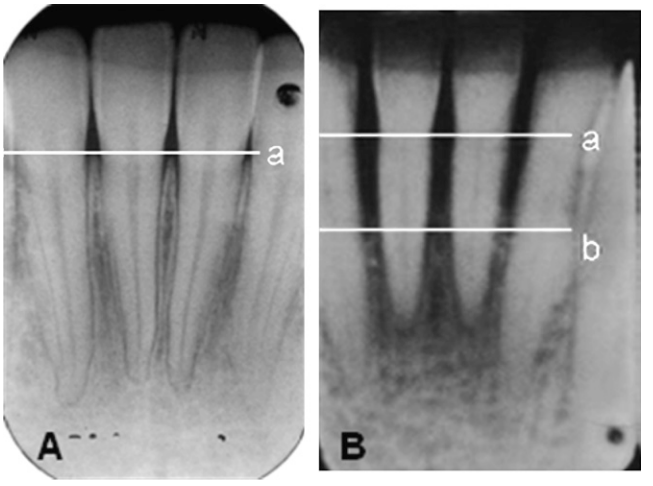

Figure 2.
In periapical x-ray ***A****, marginal bone levels* (line a) *are consistent with no history of periodontitis. In periapical x-ray* ***B****, periodontitis has caused resorption of approximately 50% to 60% of the bone supporting the mandibular anterior teeth. The approximate level of bone that would be expected in the absence of periodontitis is marked by* line a, *and the approximate level at the time of the x-ray is marked by* line b.

bacterial species, including *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* (previously *T. forsythensis*), which consistently associate with periodontitis. These bacteria activate many host immunoinflammatory processes and disrupt host mechanisms involved in bacterial clearance and are considered pathogens in periodontitis. Environmental and genetic factors as well as acquired risk factors such as diabetes mellitus and exposure to tobacco accelerate inflammatory processes in periodontitis. Although

bacteria *initiate* periodontitis, host-modifying risk factors appear to influence the severity and extent of disease.

Risk Factors (non-oral)

The following non-oral risk factors associate strongly with increased risk for periodontitis and disease severity: smoking, diabetes mellitus, genetics, mental anxiety, depression, obesity, and physical inactivity.

Individuals who smoke (cigarettes and pipes) have six to seven times more alveolar bone loss than nonsmokers in studies in the United States and other countries.[4-7] Patients with periodontitis defined by tooth attachment loss are three to five times more likely to smoke than those without attachment loss.[8] Possible mechanisms for the smoking–periodontitis relationship include increased subgingival infection by periodontal pathogens,[9] increased smoking-induced proinflammatory circulating cytokine levels such as tumor necrosis factor-alpha (TNF-α),[10] and altered collagen metabolism and wound healing.

Periodontal disease is more severe and prevalent in patients with type 1 and type 2 diabetes mellitus, on the basis of multiple domestic and global epidemiologic and clinical studies.[11] A large-scale longitudinal epidemiologic study in Pima Indians reported that the incidence of new cases of periodontitis in patients with type 2 diabetes in this ethnic population was >2.5 times greater than in non-diabetic subjects.[12] Patients with type 2 diabetes mellitus also have a faster rate of alveolar periodontal bone loss than those without diabetes with periodontitis.[13] Patients aged 10 to 18 years with type 1 diabetes mellitus have an increased prevalence of periodontitis.[14] In children and teens with diabetes, accelerated periodontal destruction relates to metabolic control.[15] Conversely, worsening periodontal disease adversely affects glycemic control.[11,13] It has been suggested that inflammation may be one mechanistic link between the two diseases.[13] Treatment of periodontal disease, especially in patients with elevated glycosylated hemoglobin, improves glycemic control.[16,17] Results from the National Health and Nutrition Examination Survey (NHANES) I and its follow-up studies suggest that non-diabetic adults with periodontal disease develop type 2 diabetes more often than those without periodontal disease.[18]

Approximately 50% of the variation in clinical severity of chronic periodontitis is explainable by genetic influences.[19] The first report of association with specific gene variants involved the interleukin (IL)–1 gene cluster,[20] but other identified genetic factors are also likely to contribute to periodontitis.[1]

Treatment

All appropriate treatment strategies for periodontitis focus on the resolution of gingival inflammation and healing of the soft and hard tissue attachment of the teeth to the alveolar process by removal of the bacterial biofilm attached to the tooth roots and reinforcement of patient oral hygiene to reduce bacterial regrowth.

Systemic antibiotics may be used as an adjunct to conventional bacterial removal in severe periodontitis and in patients with host-modifying risk factors, such as diabetes mellitus.[21] Antibiotics locally delivered into the periodontal pockets have been approved by the United States Food and Drug Administration (FDA) as an adjunct to conventional bacterial removal in the management of periodontitis. Antibiotics markedly reduce the bacterial load but taken alone do not usually eliminate periodontal pathogens in the oral cavity. Antibiotics may transiently improve localized sites of periodontitis when combined with mechanical debridement to disrupt the subgingival biofilm.

Host-modulating drugs that reduce the clinical signs and symptoms and progression of periodontitis have been evaluated, and the matrix metalloproteinase inhibitor low-dose *doxycycline* is the only FDA-approved host-modulating drug for the treatment of periodontitis. Other host-modulating agents that hold promise but are not currently approved for use in periodontal therapy include non-steroidal anti-inflammatory drugs (systemic [flurbiprofen] and topical [ketorolac]), bisphosphonates (alendronate sodium), and resolvins.

Advanced periodontitis (moderate to severe bone loss and gingival probing depth >5 mm) may require surgery to gain adequate access for removal of the bacterial biofilm and residual calculus on the root surfaces. In some instances, surgical approaches include bone and soft tissue regeneration to regain at least some support for the teeth and to facilitate bacterial control.

Prevention

Long-term clinical studies have clearly demonstrated that the regular and effective removal of bacterial biofilms on the teeth can prevent periodontitis.[22] Effective removal requires excellent oral hygiene, including interproximal cleaning and periodic professionally administered biofilm removal.[23,24]

INFLAMMATION AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

The dietary ingestion of low-density lipoprotein (LDL), mainly from animal fat, with subsequent lipid oxidation and accumulation of lipid products within the arterial vascular wall is essential for atherogenesis. Thus, the most important current strategies for preventing atherosclerotic CVD are dietary fat restriction and pharmacologic measures that lower serum levels of LDL cholesterol. A number of risk factors also relate closely to the development of atherosclerotic

disease and risk for cardiovascular events (e.g., myocardial infarction and stroke), including age, gender, hypertension, diabetes mellitus, smoking, and low serum levels of high-density lipoprotein (HDL) cholesterol.[25,26]

Over the past 2 decades, inflammation has emerged as an integrative CVD factor. Inflammation can operate in "all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis."[27] Higher quantiles of CRP, measured by a high-sensitivity assay (hsCRP), predict future acute myocardial infarction and unstable angina pectoris[28,29] and the onset of systemic arterial hypertension, diabetes mellitus, and stroke,[30-32] independent of blood lipid levels.[33] CRP itself, beyond serving as a biomarker, may have a role in endothelial cell dysfunction.[33-35] The erythrocyte sedimentation rate, chemokines, and cytokines including IL-6, IL-8, IL-10, IL-18, TNF-α, and monocyte chemoattractant protein–1 also are frequently abnormal in patients with acute coronary syndromes[36-38] and in many other conditions. The incidence of atherosclerotic CVD events increases in patients with chronic inflammatory diseases, in addition to periodontitis, including rheumatoid arthritis,[39] psoriasis,[40] systemic lupus erythematosus,[41,42] and some types of infections, mainly infections of the respiratory tract and urinary tract.[43] Arterial inflammation, along with arterial stiffness and remodeling, may be a factor in systemic arterial hypertension,[44-54] particularly in obese patients. Evidence supporting the role of inflammation in atherosclerotic events gained support with the findings of Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER),[55] in which treatment with rosuvastatin significantly reduced the incidence of cardiovascular events in subjects with lower levels of LDL cholesterol but with mild chronic inflammation indicated by levels of hsCRP >2 mg/L. The precise role of inflammation as a *direct, causative* factor in chronic atherogenesis and in the acute complications of atherosclerosis remains an area of intense current investigation.[35,56,57]

PERIODONTITIS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

The association between periodontitis and atherosclerotic CVD has received considerable attention.[58-91] The findings of these studies, however, have varied greatly, ranging from determinations of no causative relationship between periodontitis and CVD to strong causative connections between the two conditions. Reasons for the discrepancies in the results of these studies include[73] (1) variations in study populations, including differing age groups, ethnicities, and geographic locations, and (2) differing measures and definitions of periodontitis, with some studies based only on clinical measures (i.e., probing depth, bleeding on probing, tooth attachment level) and other studies, in which the relationship appeared stronger, based on non-clinical measures such as systemic antibody response[71] or radiographic evidence of alveolar bone loss. Increased carotid artery intimal-medial thickness measured by ultrasound, which is associated with increased risk for acute myocardial infarction and stroke in subjects without histories of CVD,[76] often occurs in patients with periodontitis, suggesting that subclinical atherosclerosis is present in many patients with periodontitis.[77,78]

Coronary Artery Disease (CAD)

Although some past studies have not supported a causal relationship between periodontitis and CAD,[77,87] a meta-analysis[92] of data linking CAD and periodontitis concluded that periodontal disease is a risk factor or marker independent of traditional CAD risk factors, with relative risk estimates ranging from 1.24 to 1.35. Another meta-analysis[93] also found significantly increased prevalence and incidence of CAD in patients with periodontitis, again raising the possibility that periodontitis independently predicts CAD. The two meta-analyses concluded, however, that further studies are needed to better define the relationship between the two diseases. Analysis of >1,200 men in the Veterans Affairs Normative Aging and Dental Longitudinal Studies[62] determined that in men aged <60 years, there was a "significant dose-dependent association" between CAD prevalence and periodontitis, with a hazard ratio of 2.12 (95% confidence interval 1.26 to 3.30) when using clinical and radiographic criteria for periodontitis. This association was independent of standard atherosclerotic CVD risk factors or socioeconomic status. In men aged >60 years, however, the dose-dependent association between CAD and periodontitis was absent in this study. Periodontitis prevalence also has been correlated with angiographic evidence of CAD.[63]

Cerebrovascular Disease

Analysis of NHANES I[94] and the NHANES Epidemiologic Follow-Up Study (NHEFS)[94] found that periodontal disease is an important risk factor for all forms of cerebrovascular disease, especially non-hemorrhagic stroke. Data from the Health Professionals Follow-Up Study (HPFS), which involved >50,000 male health professionals, revealed that periodontal disease and fewer teeth at baseline correlated with increased risk for stroke during the subsequent 12-year follow-up period.[95] Some studies, however, have not found a relationship between periodontitis and cerebrovascular disease.[2,77]

Table 1.

Confidence and Evidence Codes

Confidence	Description
1	Very confident
2	Confident
3	Marginally confident
4	Not confident
Type of evidence	
A	Well-designed RCT conducted in patients who have reported adverse experiences.
B	Single RCT with a highly statistically significant result.
	Well-conducted retrospective case-control studies with adverse experiences as primary end points.
	Managed care claims database analysis with a highly statistically significant result.
C	Reports to regulatory agencies judged to exceed population averages and reporting bias.
	Multiple case studies with non-blinded dechallenge and rechallenge.
	Strong trends, not reaching statistical significance, for safety issues in large RCTs.
	Well-conducted prospective cohort study, giving a result that is statistically well above population average.
	Metabolic or clinical surrogate studies.
D	Undocumented opinion of experienced research investigators and clinicians.
	Poorly controlled or uncontrolled studies.
	Non-definitive evidence from regulatory agency reporting systems or managed care claims databases.
U	Unknown, no appropriate evidence, or evidence considered subject to bias.

RCT = randomized controlled trial.

Peripheral Arterial Disease

A small study reported a direct link between peripheral arterial disease and periodontitis, which related the two conditions in association with increases in the serum cytokines IL-6 and TNF-α.[96] Another study of peripheral arterial disease in 212 young women (mean age 48 ± 7 years) found an independent relationship between peripheral arterial disease and a history of periodontitis, unaffected by the level of hsCRP.[97]

MECHANISMS FOR AN ASSOCIATION BETWEEN PERIODONTITIS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

A *direct* causal relationship between periodontitis and atherosclerotic CVD is not established. Multiple studies, however, support two biologically plausible mechanisms:[98-101] (1) Moderate to severe periodontitis increases the level of systemic inflammation, a characteristic of all chronic inflammatory diseases, and periodontitis has been associated with increased systemic inflammation as measured by hsCRP and other biomarkers. Treatment of moderate to severe periodontitis sufficient to reduce clinical signs of the disease also decreases the level of systemic inflammatory mediators.[100,101] (2) In untreated periodontitis, 10^8 to 10^{12} gram-negative bacteria may be found in periodontal pockets surrounding each diseased tooth and in approximation to ulcerated epithelium, and bacterial species found predominantly in the periodontal pockets also have been found in atheroma.[99]

An *indirect* relationship between periodontitis and atherosclerotic CVD is the many shared risk factors that commonly occur in the two diseases. Thus, many factors, especially cigarette smoking,[5-10] are confounders in determining their relative importance in this relationship. There is evidence that periodontal disease is related to CVD in young (aged ≤55 years) non-smokers.[91] In addition to tobacco use, the following risk factors are common to periodontitis and CVD: (1) Diabetes mellitus: there are no reported interventional studies designed to ascertain whether periodontal disease prevention or treatment reduces CVD prevalence or mortality in patients with either type 1 or type 2 diabetes mellitus. (2) Obesity: systemic inflammation, defined by increased circulating TNF-α, is associated with obesity and periodontitis and has been proposed as a mechanism for the connection between these conditions.[102,103] Systemic inflammatory responses also could explain the association between periodontitis and type 2 diabetes by cytokine-induced insulin resistance. (3) Lipids: a case-controlled study showed that periodontitis is associated with elevated plasma triglycerides and total cholesterol.[104] A large epidemiologic study in the United States determined that total serum cholesterol and plasma levels of CRP and fibrinogen are elevated in patients with periodontitis.[87] Other epidemiologic studies in Japan[105] and Germany[104] also found that dyslipidemia is more common in patients with periodontitis. (4) Hypertension: an epidemiologic study in Sweden of >4,000 subjects showed an increased prevalence of hypertension in patients with periodontitis.[106] Smaller studies in the United States found that, after adjusting for confounders, hypertension was more prevalent in patients with severe alveolar bone loss,[107] and significantly more hypertension occurs in patients with periodontitis compared with populations with little or no periodontal disease.[108] Whether hypertension is a risk factor for periodontitis, however, remains uncertain. Systemic inflammation, a feature of hypertension, as evidenced by increased hsCRP plasma levels in patients with prehypertension and patients with established hypertension,[32] may link these two conditions.

Major depression, physical inactivity, family histories of CVD and periodontal disease, advancing age, and male gender are other risk factors for atherosclerotic CVD that are commonly found in patients with periodontitis and also may serve as confounders.

CLINICAL RECOMMENDATIONS: PATIENTS WITH PERIODONTITIS

Although the treatment of periodontitis reduces systemic markers of inflammation and endothelial dysfunction, no prospective periodontitis intervention studies have evaluated CVD outcomes. It seems reasonable, however, on the basis of current data, to acknowledge that because untreated or inadequately controlled moderate to severe periodontitis increases the systemic inflammatory burden, periodontitis *may* independently increase the risk for CVD. (See Table 1 for confidence and evidence level codes.)

I. Patient Information

Recommendation A: Patients with moderate to severe periodontitis should be informed that there may be an increased risk for atherosclerotic CVD associated with periodontitis.

Confidence and evidence level: 2C

Recommendation B: Patients with moderate to severe periodontitis who have one known major atherosclerotic CVD risk factor, such as smoking, immediate family history of CVD, or history of dyslipidemia, should consider a medical evaluation if they have not done so in the past 12 months.

Confidence and evidence level: 3D

Recommendation C: Patients with periodontitis who have ≥2 known atherosclerotic CVD major risk factors should be referred for medical evaluation if they have not done so in the past 12 months.

Confidence and evidence level: 2D

II. Medical and Dental Evaluations

In concert with the following recommendations, it is recommended that patients with periodontitis assess their risk for future (next 10 years) CVD events (e.g., stroke, myocardial infarction) by completing either the Reynolds Risk Score[109] (*http://www.reynoldsriskscore.org*) or, for risk assessment for CAD events only, the National Cholesterol Education Program Risk Calculator (*http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof*), based on the Framingham Heart Study.

Recommendation A: Medical evaluation of patients with periodontitis should include assessment of atherosclerotic CVD risk, including past CVD events, and family histories of premature atherosclerotic CVD disease or sudden coronary death, diabetes mellitus, systemic hypertension, or dyslipidemia.

Confidence and evidence level: 2D

Recommendation B: Medical evaluation of patients with periodontitis should include a complete physical examination and annual measurement of blood pressure at rest (seated for 5 minutes with the feet on the floor and attention to appropriate blood pressure cuff size).

Confidence and evidence level: 2D

Recommendation C: Medical evaluation of patients with periodontitis should include a blood lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and fasting triglycerides) and blood glucose measurement. A plasma hsCRP determination is optional but should be considered, because recent studies have suggested that elevated plasma hsCRP may have added value by helping determine how aggressively standard risk factors should be treated, especially lifestyle changes.[57,110,111]

Confidence and evidence level: 2D

III. Risk Factor Treatment: Abnormal Lipids

Recommendation A: Patients with periodontitis and ≥1 abnormal serum lipid and/or elevated plasma hsCRP are recommended to follow a multifaceted lifestyle approach to reduce atherosclerotic CVD risk according to the National Cholesterol Education Program Adult Treatment Panel III guidelines.[112]

Confidence and evidence level: 1C

According to Adult Treatment Panel III guidelines, emphasis on weight loss and physical activity to enhance weight reduction in subjects with elevated serum LDL cholesterol should be undertaken. Goals for LDL cholesterol levels are based on CVD risk assessment: (1) one atherosclerotic CVD risk factor and LDL cholesterol >160 mg/dl: target LDL cholesterol <160 mg/dl; (2) ≥2 atherosclerotic CVD risk factors and LDL cholesterol >130 mg/dl: target LDL cholesterol <130 mg/dl; an optional target is LDL cholesterol <100 mg/dl if factors such as age, metabolic syndrome, abnormal plasma hsCRP, or abnormal coronary calcium score (75th percentile) are present; (3) atherosclerotic CVD disease is present or there are CAD risk equivalents, such as diabetes mellitus: target LDL cholesterol <100 mg/dl or an optional target of <70 mg/dl if atherosclerotic CVD is present and there are high-risk features, such as diabetes mellitus, metabolic syndrome, heavy cigarette smoking, or acute coronary syndromes.

Lifestyle changes that should be undertaken are reduced intake of saturated fats (<7% of total calories) and low levels of trans fats and dietary cholesterol (<200 mg/day); enhancement of LDL lowering with optional dietary strategies, such as ingesting plant stanols or sterols (2 g/day) and increased viscous (soluble) fiber (10 to 25 g/day); weight reduction; increased physical activity; and limited alcohol

ingestion (''*Moderation* is defined as the consumption of up to one drink per day for women and up to two drinks per day for men. Twelve fluid ounces of regular beer, 5 fluid ounces of wine, or 1.5 fluid ounces of 80-proof distilled spirits count as one drink. This definition of moderation is not intended as an average over several days but rather as the amount consumed on any single day."[112]) However, alcohol does not add to atherosclerotic CVD risk and may convey some protective effect against future CVD events. Patients who need to lose weight should be cautioned, however, that alcohol is high in caloric content. Subjects who do not drink alcohol should not be advised to begin drinking alcohol for the purpose of CVD risk modification, because other risks of alcohol consumption, such as higher frequencies of accidents and medical illnesses, outweigh the possible CVD-preventive benefits of alcohol.

Recommendation B: Drug therapy for elevated LDL cholesterol should be prescribed in patients with periodontitis in whom target LDL cholesterol levels are not achieved with lifestyle changes.

Confidence and evidence level: 2D

IV. Risk Factor Treatment: Cigarette Smoking

Recommendation: All patients with periodontitis who smoke tobacco should discontinue this habit because this is a major risk factor for atherosclerotic CVD and periodontitis.

Confidence and evidence level: 1C

V. Risk Factor Treatment: Hypertension

Recommendation A: All patients with periodontitis and elevated blood pressure should be treated to target levels as defined by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7).[25]

Confidence and evidence level: 1C

JNC-7 defines hypertension as follows: (1) *prehypertension*: systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg; (2) *stage 1 hypertension*: systolic blood pressure 140 to 159 mm Hg or diastolic blood pressure 90 to 99 mm Hg; and (3) *stage 2 hypertension*: systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg. Using JNC-7 recommendations, the target blood pressures in patients with periodontitis are (1) <140/90 mm Hg in all patients with periodontitis and ≤2 major risk factors for CAD and (2) <130/80 mm Hg in patients with previous atherosclerotic CVD, diabetes mellitus, chronic renal disease, or ≥3 major risk factors.

Recommendation B: All patients with periodontitis and elevated blood pressure should undertake lifestyle changes.

Confidence and evidence level: 1A

Elevated blood pressure can be significantly decreased by lifestyle changes, including (pressures in parentheses indicate changes that can be anticipated with adequate patient compliance) weight reduction in subjects who are overweight (systolic blood pressure reduction 5 to 20 mm Hg), a diet high in potassium and calcium (the American Heart Association DASH diet;[113] systolic blood pressure reduction 4 to 8 mm Hg), a diet low in sodium (systolic blood pressure reduction 2 to 8 mm Hg), physical activity (systolic blood pressure reduction 4 to 9 mm Hg), and moderation of alcohol intake (systolic blood pressure reduction 2 to 4 mm Hg).

In addition to lowering blood pressure, lifestyle modifications also increase the efficacy of antihypertensive drug therapy and decrease the risk for atherosclerotic CVD.

Recommendation C: All patients with periodontitis and elevated blood pressure not controlled to target levels with lifestyle changes should be treated with pharmacologic therapy.

Confidence and evidence level: 2D

The following drug classes are approved for the initial treatment of hypertension: thiazide-type diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, β blockers, and calcium channel blockers (see recommendation D).

Recommendation D: Patients with periodontitis prescribed calcium channel blockers for hypertension or any other indication should be monitored for worsening of periodontitis in association with gum hyperplasia.

Confidence and evidence level: 1D

Gingival hyperplasia has been reported with all three classes of calcium channel blockers.[114] This effect is reported most often with nifedipine, occurring in up to 6% of patients,[115] and less often with diltiazem, amlodipine,[116,117] and verapamil.[118,119] The mechanism is unknown but may be due to increased gingival collagen production by fibroblasts.[120] However, there are no specific reports of the effect of calcium channel blockers on the severity of periodontitis.

VI. Risk Factor Treatment: Metabolic Syndrome

Metabolic syndrome is diagnosed when ≥3 of the following features are present: (1) increased waist circumference (men ≥40 in [≥102 cm], women ≥35 in [≥88 cm]), (2) increased serum triglyceride level (150 mg/dl [1.7 mmol/L]) and/or drug treatment for elevated triglycerides (most commonly fibrates and nicotinic acid), (3) decreased serum HDL cholesterol level (men <40 mg/dl [1.03 mmol/L], women <50 mg/dl [1.3 mmol/L]) and/or drug treatment for decreased serum HDL cholesterol, (4) elevated blood pressure

(≥130 mm Hg systolic and/or ≥85 mm Hg diastolic) or antihypertensive drug treatment of patients with histories of hypertension, and (5) elevated fasting glucose (blood glucose ≥100 mg/dl) and/or drug treatment for hyperglycemia.

Recommendation: Patients with periodontitis meeting criteria for metabolic syndrome should be identified, and all risk factors for atherosclerotic CVD should be treated, beginning with lifestyle changes aimed at weight reduction.

Confidence and evidence level: 1D

Metabolic syndrome is closely linked to insulin resistance and is a secondary target of lipid therapy because the risk factors for metabolic syndrome are highly concordant and, in aggregate, enhance the risk for atherosclerotic CVD at any serum level of LDL cholesterol.[121] *Many patients with periodontitis meet criteria for the metabolic syndrome.*[103] Because measures of systemic inflammation are a common feature of periodontitis and metabolic syndrome, it may be particularly important to identify patients who meet these criteria for CVD prevention strategies.

VII. Special Considerations in the Treatment of Atherosclerotic CVD in Patients With Periodontitis

No reported studies present evidence that patients with periodontitis and atherosclerotic CVD should receive different treatment from other patients with CVD, with the possible exception of the use of calcium channel blockers. Recent studies suggest that standard treatments of periodontitis in patients with CVD are effective.[122] The panel did make special note that additional studies are needed regarding the effect of other drugs used in cardiovascular medicine on periodontitis. There is, however, no conceptual basis for concern that any current standard treatment for periodontitis should be altered in patients with concurrent atherosclerotic CVD.

CLINICAL RECOMMENDATIONS: PATIENTS WITH ATHEROSCLEROTIC CARDIOVASCULAR DISEASE WITH OR WITHOUT A PREVIOUS DIAGNOSIS OF PERIODONTITIS

I. Patients With Atherosclerotic CVD and Previous Diagnosis of Periodontitis

Recommendation: Periodontists and physicians managing patients with CVD should closely collaborate to optimize CVD risk reduction and periodontal care.

Confidence and evidence level: 1D

II. Patients With Atherosclerotic CVD and No Previous Diagnosis of Periodontitis

Recommendation A: Periodontal evaluation should be considered in patients with atherosclerotic CVD who have signs or symptoms of gingival disease, significant tooth loss, and unexplained elevations of hsCRP or other inflammatory biomarkers.

Confidence and evidence level: 2D

Recommendation B: Periodontal evaluation of patients with atherosclerotic CVD should include a comprehensive examination of periodontal tissues, as assessed by visual signs of inflammation and bleeding on probing, loss of connective tissue attachment detected by periodontal probing measurements, and bone loss assessed radiographically. If patients have untreated or uncontrolled periodontitis, they should be treated with a focus on reducing and controlling the bacterial accumulations and eliminating inflammation.

Confidence and evidence level: 2D

Recommendation C: When periodontitis is newly diagnosed in patients with atherosclerotic CVD, periodontists and physicians managing patients' CVD should closely collaborate to optimize CVD risk reduction and periodontal care.

Confidence and evidence level: 1D

RECOMMENDATIONS FOR FUTURE RESEARCH

Although the inflammation hypothesis provides a plausible and attractive explanation for the periodontitis–atherosclerosis relationship, further research is needed to define the mechanisms linking the two diseases and how patients with periodontitis should best be managed to reduce their risk for CVD. Specific questions that the consensus panel believes should be addressed in future research include the following: (1) Is periodontitis an independent risk factor for atherosclerotic CVD? (2) If periodontitis is an independent risk factor for atherosclerotic CVD, what is the mechanism of the relationship, and at what stage(s) of atherogenesis is it important? (3) Regardless of whether periodontitis is an independent risk factor for atherosclerotic CVD, should risk factors for atherosclerotic CVD be treated more aggressively in patients with periodontitis than current guidelines recommend for the general population? (4) Do periodontal therapeutic interventions, such as infection and inflammation control, directly reduce the rate of atherosclerotic plaque development and its complications, especially acute myocardial infarction and stroke? (5) Because periodontitis in the general population is greatly underdiagnosed and undertreated, what measures can improve its detection and management in persons at increased risk for primary and secondary atherosclerotic CVD events? (6) Are there specific oral microbial pathogens that add to CVD risk and therefore should be targeted for antibiotic treatment? (7) In addition to the possible role of periodontal inflammation caused by infection, does secondary endotoxemia play a causative role in the relationship between periodontitis and atherosclerotic

CVD? (8) Are acute events such as acute myocardial infarction and stroke more likely to occur during periods of worsening periodontitis? (9) Do calcium channel blockers have any adverse effect on periodontitis other than causing gingival hyperplasia in some persons, and if so, what is the magnitude of this effect? (10) In addition to calcium channel blockers, are there other cardiovascular medications that may adversely affect periodontitis?

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