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Lipoproteins and lipoprotein metabolism in periodontal disease

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Abstract

A growing body of evidence indicates that the incidence of atherosclerosis is increased in subjects with periodontitis – a chronic infection of the oral cavity. This article summarizes the evidence that suggests periodontitis shifts the lipoprotein profile to be more proatherogenic. LDL-C is elevated in periodontitis and most studies indicate that triglyceride levels are also increased. By contrast, antiatherogenic HDL tends to be low in periodontitis. Periodontal therapy tends to shift lipoprotein levels to a healthier profile and also reduces subclinical indices of atherosclerosis. In summary, periodontal disease alters lipoprotein metabolism in ways that could promote atherosclerosis and cardiovascular disease.

Keywords

high-density lipoprotein; low-density lipoprotein; oxidized LDL; periodontal disease; periodontal therapy; periodontitis; *Porphyromonas gingivalis*; triglyceride

Despite years of effort and a countless amount of money spent on research, cardiovascular disease remains one of the leading causes of morbidity and mortality in the world [1,2]. Underlying cardiovascular disease is the process of atherosclerosis, a biological response that is akin to inflammation [2–4]. Although it has long been recognized that dyslipidemia is an underlying cause of atherosclerosis, recent investigations suggest that chronic inflammation is also involved. Systemic markers of inflammation such as IL-6 and C-reactive protein (CRP) are elevated in the plasma of atherosclerosis patients [5,6]. Inflammation is an important part of the innate immune response against pathogens. These correlations are the underpinning of the concept that chronic infection/chronic inflammation both promote and exacerbate atherosclerosis. Indeed, a variety of infectious agents, most notably *Chlamydia pneumoniae*, *Helicobacter pylori*, *Trypanosoma cruzi* and Herpes simplex virus, have been linked to atherosclerosis in recent years [4,7,8]. These studies have prompted a re-examination of the list of risk factors for cardiovascular disease that was originally compiled by the Framingham study in the 1960s.

This article is focused on the correlation between atherosclerosis and periodontitis a chronic inflammatory disease of the oral cavity that is of infectious origin. Periodontal disease has been cited as one of the most prevalent infectious diseases that afflicts humankind [9,10]. In recent

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years, a variety of studies have correlated periodontitis with atherosclerosis and vascular disease, using indices such as circulating mediators of inflammation (IL-6 and CRP), evidence of infection with oral pathogens (bacterial DNA and antibodies against oral bacteria) and clinical evidence of periodontal disease as markers [11–44]. Although associations are typically modest, most studies support the concept that the chronic inflammation inherent in periodontal disease predisposes susceptible individuals to developing atherosclerosis. The purpose of this article is to delineate the changes in lipoprotein metabolism that occur in periodontitis and discuss their impacts on development/progression of atherosclerosis.

Periodontal disease

Periodontal disease consists of a family of infectious diseases of the oral cavity that are among the most prevalent chronic infections known. Estimates of its prevalence are as high as 75% in the USA, with some studies suggesting that severe periodontitis occurs in more than 30% of individuals over 50 years of age [11–13,45]. Although periodontal diseases are classified into different categories based on molecular mechanisms of pathogenesis, they are all characterized by severe destruction of the supporting structures of the teeth. The pathogenesis of periodontal disease starts with chronic infection with one or more bacterial pathogens. Typically, oral pathogens are Gram-negative bacteria, often anaerobes, that colonize the biofilm that forms at the gum line. A variety of Gram-negative bacteria have been linked to the pathogenesis of periodontal disease, most notably *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* [4,9]. In the initial stages of the infection, the inflammatory response results in gingivitis, which is characterized by swelling, redness and bleeding of the gums. Persistent infection leads to a chronic inflammatory response that culminates in destruction of the periodontal ligament, destruction/resorption of alveolar bone and eventual tooth loss. Typically monitored clinical manifestations of periodontal disease include gingival bleeding on probing (BOP), pocket depth (PD), clinical attachment loss (CAL) and alveolar bone loss [46]. Although these clinical manifestations are shared by all of the destructive forms of periodontal disease, these disorders differ in their etiology, the relative contributions of environmental/genetic factors and the rate of attachment loss/bone destruction. Seven major categories of disease were recognized by the most recent International Workshop on the Classification of Periodontal diseases (1999) [47,48]:

- Gingival diseases (involving inflammation of the gingiva but no loss of connective tissue/bone);
- Chronic periodontitis (typically adult onset, slowly progressing loss of connective tissue/bone in medically healthy individuals; can present as localized or generalized disease);
- Aggressive periodontitis (typically juvenile onset, rapidly progressing loss of connective tissue/bone in medically healthy individuals; can present as localized or generalized disease);
- Periodontitis as a manifestation of systemic disease (including hematological disorders, genetic and metabolic diseases);
- Necrotizing periodontal disease (including necrotizing periodontitis and necrotizing gingivitis);
- Abscesses of the periodontium (gingival, periodontal and pericoronal abscesses);
- Combined periodontal–endodontal lesions.

Periodontal disease, atherosclerosis & cardiovascular disease

Although associations tend to be modest, periodontitis has been correlated with a variety of systemic diseases, including the metabolic syndrome [49–51], insulin resistance [52] and pre-term birth/low birth weight [53,54]. During the past decade, an enormous amount of literature has emerged linking periodontal disease with atherosclerosis and vascular disease [11–44]. Such studies are rooted in literature demonstrating linkages between infection, chronic inflammation and atherosclerosis [8,55–57]. Although the mechanism underlying the connection between atherosclerosis and periodontal disease remains somewhat obscure, oral pathogens have been shown to activate the major cell types involved in atheroma development, including endothelial cells [58–62], smooth muscle cells [63,64], monocytes [65–68] and platelets [69,70].

The correlation between periodontitis and atherosclerosis is substantiated by meta-analyses of the existing literature that have recently been published [11,12]. In a review of the literature in 2005, Offenbacher and Beck concluded that 80% of cross-sectional, longitudinal and case–control studies reported associations between periodontal disease and measures of atherosclerosis/vascular disease [13], an outcome that also holds true in more recent studies. For example, the odds ratio for coronary heart disease was reported to be 1.5 among dentulous individuals in the Atherosclerosis Risk in Communities (ARIC) cross-sectional study [14]. Although this association may vary with age [15], these observations support the concept that chronic inflammation/infection of the oral cavity impacts on systemic vascular health. This conclusion also holds true in investigations into the correlation between periodontal disease and myocardial infarction, which demonstrate modest associations between the incidence of myocardial infarction and clinical indices of periodontal disease [16–18]. Interestingly, reported odds ratios vary depending on the clinical index studied, with the highest ratios being reported for PD. There are also reports of increased myocardial infarction in edentulous subjects, an indirect indication that periodontitis predisposes subjects to develop vascular disease [14,15]. Edentulism has also been correlated with risk of stroke/transient ischemic attack in the ARIC study [71]. Together, these studies suggest a modest correlation between periodontitis and clinical indices of vascular disease.

Another body of literature demonstrates even stronger associations between periodontal disease and subclinical measures of atherosclerosis/vascular disease. For example, coronary artery calcification correlates with severe periodontitis in subjects in the ARIC study [19]. Other studies have correlated plaque accumulation, gingival inflammation and severe periodontitis with intima-media thickness (IMT) or intima-media area of the common carotid and internal carotid arteries, with odds ratios reported to be as high as 5.20 [20–24]. Dentate subjects with severe periodontal bone loss exhibit increased carotid plaque thickness. Carotid plaque thickness has been correlated with tooth loss in subjects in the Oral Infections and Vascular Disease Epidemiology Study [25,26]. Interestingly, there is some evidence that these associations may be gender-specific, as carotid artery plaque presence correlates with tooth loss and periodontitis in males but not females [27]. Severe periodontitis has also been linked to peripheral vascular disease in studies correlating ankle–brachial index with CAL and in studies that identify oral pathogens in peripheral atheromas [28,29]. Conversely, a subclinical measure of periodontal disease, the presence of antibodies against oral pathogens, has been correlated with indices of atherosclerosis/cardiovascular disease. In the ARIC study, IgG antibodies against *Campylobacter rectus* were correlated with increased IMT and the prevalence of IMT greater or equal to 1 mm was approximately twice as high in subjects positive for anti-*C. rectus* and anti-*Peptostreptococcus* antibodies [30]. Pussinen *et al.* reported a significant correlation between anti-*P. gingivalis* antibodies and stroke, with an odds ratio of 3.31 for nonsmoking men [31].

A growing body of literature has correlated periodontal disease with circulating mediators of inflammation/atherosclerosis. More than a decade ago, Ebersole and colleagues reported increased high-sensitivity CRP (hsCRP) in subjects with adult periodontitis [32]. More recent studies have not only confirmed this observation, but have demonstrated additional associations between severe periodontitis and soluble VCAM, soluble ICAM, soluble E-selectin, platelet activation, tissue plasminogen activator, plasma fibrinogen, IL-6, TNF-α and serum amyloid protein A [29,33–43]. Interestingly, hsCRP levels have been correlated with both periodontitis and gingivitis, suggesting that this marker of inflammation is elevated even before the onset of frank periodontitis [44,72].

Conversely, oral health tends to be compromised in patients with cardiovascular disease. In a twin study, increased BOP, horizontal bone loss and increased periodontal pockets over 4 mm in size were observed in subjects with coronary heart disease [73]. Coronary heart disease has also been correlated with an increase in the number of plaque-positive sites, increased PD and increased numbers of missing teeth [74]. Subjects with acute myocardial infarction are reported to have increased numbers of missing teeth and an increase in periodontal screening index – a measure of the severity of periodontal disease [75]. Together, these studies highlight the bidirectional nature of the relationship between severe periodontitis and cardiovascular disease – a relationship that may stem from a genetic predisposition to hyperinflammatory responses [76]. This supposition is borne out by the recent identification of a genetic susceptibility locus that is shared by both aggressive periodontitis and heart disease [77].

Among the major challenges of these studies is the need to establish a causal relationship between periodontal disease and atherosclerosis. Although this question can be approached by investigating whether periodontal therapy reduces vascular disease, such studies cannot include untreated controls (for ethical reasons) and, therefore, are imperfect mechanisms to test for causality. There are also concerns regarding the clinical/subclinical parameters used to define periodontal disease and vascular disease, which vary between studies and do not always correlate with active disease [46,78–81]. As noted above, some researchers have reported that associations are strongest between periodontal disease and subclinical measures of atherosclerosis [11]. Furthermore, there is evidence that markers of oral infection (antibodies against oral pathogens and bacterial DNA) may be more consistently correlated with atherosclerosis than clinical indices of periodontal disease [80]. In short, this is a relatively new area of investigation and there is a need for standardization and the implementation of more comprehensive longitudinal studies in order to uncover the mechanisms underlying the correlation between atherosclerosis and periodontitis.

Lipoproteins

Lipoproteins are macromolecular particles that are the major mechanism for the transport of insoluble lipids in the plasma. The various classes of lipoproteins are composed of lipid-binding apolipoproteins embedded in a monolayer of phospholipid and free cholesterol that surrounds a neutral lipid core comprised of triacylglycerols (TGs) and cholesteryl esters (CE). VLDLs are characterized by a TG-rich core and the presence of apolipoproteins B, C and E. There are two distinct species of VLDL; VLDL-I and VLDL-II, which differ in their TG content (Table 1). ApoCII activates lipoprotein lipase, which hydrolyzes TG and thereby converts VLDL to intermediate-density lipoprotein (IDL). Cholesterol ester transfer protein (CETP) facilitates the transfer of CE from HDL to IDL and moves TG and phospholipids from IDL to HDL, resulting in the formation of LDLs. LDL particles contain approximately 1500 molecules of CE, 800 molecules of phospholipid, 500 molecules of free cholesterol and a single molecule of ApoB100 [82]. LDL species are classified into four groups based on size, density, charge, lipid content and apolipoprotein content [83]. These groups are denoted as LDL-I, -II, -III, –IV and -V, and range from large, buoyant LDL to small, dense LDL (LDL-IV and LDL-V)

(Table 1) [84,85]. Subjects with a prevalence of small, dense LDL particles (sdLDL) who also have high TG and low HDL-C (the 'atherogenic lipid triad') are at increased risk for cardiovascular disease [85–89], in part because sdLDLs have reduced receptor uptake, allowing longer time in the circulation [90], increased proteoglycan binding, allowing increased retention in the arterial wall [91], and are more susceptible to oxidation [92].

The major function of HDL is the transport of cholesterol from peripheral tissues to the liver through the process of reverse cholesterol transport [93]. Although HDL has traditionally been classified into two subspecies (HDL-2 and HDL-3) based on density, recent studies suggest that the HDL pool is very complex, consisting of multiple subspecies with varying lipid and lipoprotein content [94]. Common to all HDL species is ApoA-I. While elevated plasma LDL is associated with increased risk of atherosclerosis, elevated HDL is considered to be protective because it delivers excess cholesterol to the liver for excretion. Although the less dense, cholesterol-rich HDL-2 has generally been considered to be the more antiatherogenic subspecies, such data are relatively inconsistent, making it difficult to determine if only a particular subspecies of HDL is especially atheroprotective [94–96].

Periodontal disease, lipoproteins & lipoprotein metabolism

Dyslipidemia – abnormality in levels of TG, cholesterol, or lipoproteins in the plasma – is a hallmark of atherosclerosis, leading to cardiovascular disease. Although other factors (e.g., chronic inflammation) are now known to contribute to pathogenesis, dyslipidemia is still noted for its causal relationship with the disease [97–100]. There are reports to the contrary [101–103], but most studies have demonstrated elevated plasma nonesterified fatty acids, cholesterol and TG in subjects with severe periodontal disease [36,104–106]. For example, data from the Third National Health and Nutrition Examination Survey (NHANES) suggest a modest association between periodontal disease and serum cholesterol [107]. The percentage of sites with BOP has been correlated with increased total cholesterol, LDL-C and TG in diabetic subjects [108] and PD has been correlated with hypercholesterolemia, but not hypertriglyceridemia, in subjects with coronary heart disease [109]. In a recent study in Japan, an odds ratio of 2.26 was reported for the correlation between periodontal disease and elevated plasma TG (>149 mg/dl) [110]. Monteiro *et al.* also reported such an association in age-, gender- and BMI-matched subjects with chronic periodontitis [111]. Other investigators have reported that total cholesterol, LDL-C and TG are elevated in severe periodontitis [112]. Fentoglu *et al.* compared serum lipids and oral health in 51 hyperlipidemic and normolipidemic subjects. In this study, a statistically significant negative correlation was observed between HDL and CAL and statistically significant positive correlations were observed between CAL and TG, total cholesterol and LDL-C. Similar associations were observed when subjects were scored for plaque index and PD and elevated TG was also associated with increased BOP [113]. In a very recent paper, Ramirez-Tortosa *et al.* report a specific association between clinically diagnosed periodontitis and elevated VLDL-C [114]. Interestingly, only a subset of studies report reduced levels of antiatherogenic HDL in subjects with periodontitis [111,115, 116]. At present, the physiological mechanism for the potential selective effect on ApoB-containing lipoproteins is not clear. However, it may be related to changes in lipid transport and/or synthesis that occur as a result of chronic infection in the oral cavity. Recent studies suggest that the enzyme that catalyzes the rate-limiting step in cholesterol synthesis, HMG-CoA reductase, may be induced by oral pathogens [117].

The correlation between periodontal disease and dyslipidemia has also been observed in a variety of animal models. The $ApoE^{-/-}$ mouse, a well-accepted model for atherosclerosis [118,119], has been used to investigate correlations between periodontitis and dyslipidemia. These mice develop atherosclerotic lesions and exhibit increases in circulating inflammatory mediators when infected with oral pathogens (*A. actinomycetemcomitans* and *P. gingivalis*) or

infused with lipopolysaccharide (LPS) from these organisms [120–124]. These atherosclerotic responses are accompanied by decreases in particle size of VLDL, LDL and HDL, consistent with development of a 'pattern-B-like' lipoprotein profile [125,126]. Although no difference in serum cholesterol was noted, lipid accumulation was observed in aortas of New Zealand white rabbits induced to develop periodontitis in response to ligature and application of *P. gingivalis* [127]. In two recent reports, Ekuni *et al.* demonstrated lipid deposition in the descending aorta in a rat ligature-induced periodontitis model [128,129] and high cholesterol diet was shown to exacerbate periodontitis in these animals [130]. Swine maintained on a high-fat diet develop coronary and aortic atherosclerosis, which is exacerbated if the animals are infected with *P. gingivalis* [131]. Finally, Ebersole *et al.* observed increased serum cholesterol, but no change in TG in ligature-induced periodontitis in a nonhuman primate model. When placed on a high-fat diet, these animals also exhibited a transient decline in HDL [132]. Thus, animal studies support the concept of a correlation between periodontal disease and dyslipidemia, underscoring the connection between oral disease and atherosclerosis.

The presence of antibodies against oral pathogens has been correlated with indices of cardiovascular disease, such as myocardial infarction and acute coronary syndrome [133–136]. These antibodies have also been demonstrated to correlate with serum hsCRP and other markers of chronic inflammation [137]. Likewise, serum antibodies against oral pathogens have proven to be a useful marker for investigating the correlation between periodontitis and dyslipidemia. Craig *et al.* demonstrated increased total cholesterol and LDL in periodontitis subjects defined in this manner. Conversely, HDL levels were higher in antibody-negative (healthy) subjects and there was no difference in circulating TG in the two subject groups [138]. Similar results were reported by Nishimura *et al.* and Vilkuna-Rautiainen *et al.* [117, 139]. By contrast, Goteiner *et al.* reported that IgG anti-*P. gingivalis* correlates with VLDL levels but is inversely correlated with LDL in patients presenting with acute coronary syndrome, angina or noncardiac chest pain [140]. Importantly, a recent study by Beck *et al.* not only provides a direct correlation between antibodies and clinical coronary heart disease, but also suggests that antipathogen antibodies may be more reliable correlates of cardiovascular disease compared with overt periodontitis [141]. These observations are consistent with reports of oral pathogen colonization of atheromatous plaques. In recent studies, it has been reported that DNA from oral bacteria is present in 10–80% of atherosclerotic plaques [142–145]. It is important to note, however, that such correlations are not universally observed [146,147]. It is also important to note that most of the antibody studies report no correlation between TG levels and antibodies against periodontal pathogens.

A variety of confounders have been reported that impinge on the interpretation of studies correlating periodontitis with dyslipidemia. For example, Saxlin *et al.* report that the presence of periodontal pockets of more than 4 mm correlates with increased TG and reduced HDL, but only in obese subjects [148]. Katz *et al.* reported a positive correlation in periodontal pockets and serum cholesterol in male but not in female subjects [149]. Similarly, in a mouse model of periodontal disease, decreased HDL was observed only in male mice [150]. These confounders underscore the need for large, well-controlled studies in order to accurately assess the influence of periodontitis on lipoproteins and lipoprotein metabolism.

Although most studies have focused on the chronic forms of periodontitis that occur in adults, we have reported changes in the lipoprotein profiles of subjects with aggressive periodontitis – a form of the disease that typically develops during adolescence and is characterized by its rapid and aggressive progression. Elevated VLDL and IDL were observed in subjects with severe generalized aggressive periodontitis and a trend towards increased VLDL was observed in subjects with the localized form of the disease [151,152]. In addition, we observed a progressive reduction in average LDL size when compared among nonperiodontitis, localized aggressive periodontitis and generalized aggressive periodontitis subjects, suggesting a

prevalence of the atherogenic pattern-B lipoprotein profile in periodontitis subjects. Indeed, aggressive periodontitis subjects exhibited increased levels of sdLDL, a hallmark of the pattern-B lipoprotein profile [125,126]. Finally, LDLs isolated from aggressive periodontitis subjects contained less lipoprotein-associated phospholipase A_2 ($LpPLA_2$) per particle than did those from periodontally healthy subjects. This finding was consistent with our previous reports that the monocytes of aggressive periodontitis subjects have a propensity to differentiate into dendritic cells and that dendritic cells express low levels of $LpPLA_2$ [153,154]. Although the role of $LpPLA_2$ in atherosclerosis remains somewhat controversial, this observation suggests that the oxidized lipid substrates of $LpPLA_2$ might accumulate in LDLs of periodontitis patients. Such accumulation could account for the increase in lipid peroxides and oxidized LDL (oxLDL) that is observed in periodontitis [155–157]. The changes in inflammatory mediators that have been observed in aggressive periodontitis [33,39] are consistent with those reported for the chronic, adult-onset form of the disease. Additional studies are needed to confirm the correlation between aggressive periodontitis and frank cardiovascular disease and to determine if the lipoprotein profiles of chronic periodontitis subjects are shifted towards pattern B. Importantly, a recent study has demonstrated that aggressive periodontitis and heart disease share a genetic susceptibility locus [77].

Although changes in systemic lipid metabolism have been observed in other infectious/chronic inflammatory diseases [158], the mechanism underlying the correlation between chronic inflammatory disease and dyslipidemia remains obscure. The observations of Pussinen *et al.* suggest that HDL from periodontitis subjects may have a reduced capacity to extract cholesterol from macrophages and therefore to participate in reverse cholesterol transport [115]. This observation is consistent with reports of decreased expression of ATP-binding cassette transporter-1 and scavenger receptor B type I in mouse macrophages treated with *A. actinomycetemcomitans* LPS [159]. Nishimura *et al.* have demonstrated that proinflammatory cytokines (IL-6 and TNF-α) induce expression of HMG-CoA reductase [117]. As these cytokines are induced by LPS from oral pathogens [159], this observation suggests that oral bacteria may augment cholesterol synthesis. Together, these studies suggest a potential mechanism whereby periodontal infection promotes lipogenesis and thereby atherosclerosis. Other studies provide evidence that oral bacteria have direct effects on the structure/metabolism of lipoproteins. Incubation of whole blood with the oral pathogen *P. gingivalis* results in proteolysis of ApoB-100 [160]. Other investigators have demonstrated degradation of ApoB-100 by intact *P. gingivalis*, its LPS, or outer membrane vesicles from the organism [161,162]. Similar modifications are observed when *P. gingivalis* is administered to $ApoE^{-/-}$ mice [163], suggesting that these modifications may be of physiological significance. Protease inhibitors suppress *P. gingivalis*-mediated modification of LPS and these effects are attenuated when $ApoE^{-/-}$ mice are administered *P. gingivalis* lacking the Arg-gingipain, suggesting that ApoB-100 proteolysis is mediated by this highly active *P. gingivalis* protease [160,162,163]. In addition to their effects on LDL, *P. gingivalis* proteases have been linked to proteolysis of the fibrous cap that encases stable atheromas, suggesting that this oral pathogen may precipitate the penultimate event that leads to thrombosis and the clinical outcomes of atherosclerosis [164]. *P. gingivalis*-modified LDL exhibits increased mobility on SDS-PAGE and a propensity to aggregate [162,165]. Importantly, these modified LDLs exhibit increased uptake by macrophages, resulting in increased formation of the foam cells that are the basis of atherosclerotic plaque [163,166]. These observations are consistent with a report that RAW 264.7 macrophages readily ingest LDL from periodontitis subjects and that this uptake declines when subjects are successfully treated for the disease [155]. Together, these studies suggest that a variety of pathways likely lead to the increased prevalence of atherosclerosis that is observed in subjects with periodontal disease.

Another potential mechanism by which periodontal disease might exacerbate atherosclerosis is related to the antibody response against oral bacteria. As noted above, several studies have

correlated the presense of circulating antibodies against oral pathogens with cardiovascular events, including myocardial infarction and acute coronary syndrome [133–135]. Periodontitis subjects also have antibodies against lipids and lipoproteins. For example, the prevalence of β2-glycoprotein-dependent anticardiolipin is elevated in both chronic and aggressive periodontitis [155,167,168]. Other studies indicate that anti-oxLDL antibodies are elevated in subjects with periodontitis [111,169]. Levels of anti-phosphorylcholine (anti-PC) antibodies are elevated in subjects with CAL, including those with chronic and aggressive periodontitis [170]. These antibodies cross react with several species of plaque bacteria and also with oxLDL [171]. The ratio of anti-PC antibody in gingival crevicular fluid in serum indicates that much of the anti-PC is synthesized in the oral cavity, suggesting it is elicited against oral bacteria. However, there is also evidence that circulating oxLDL is elevated in periodontitis subjects [155,156], making this another potential source of anti-PC. Although the relevance of this anti-PC to atherosclerosis remains somewhat obscure, there is reason to believe that it may opsonize oxLDL and promote its uptake by macrophage-derived foam cells. oxLDL absorbs IgG anti-PC from the sera of periodontitis subjects, suggesting opsonization by this antibody [171]. It is tempting to speculate that this opsonized oxLDL binds Fc receptors on macrophages, triggering phagocytosis and thereby foam cell formation, making this another potential correlation between atherosclerosis and periodontal disease [8].

Effects of periodontal therapy on lipoproteins & lipoprotein metabolism

A growing wealth of literature investigates the effects of periodontal treatment on incidence and severity of periodontal disease. Although some reports suggest the contrary [172], most studies indicate that treatment not only reduces indices of periodontal disease but also ameliorates atherosclerosis. In the $ApoE^{-/-}$ mouse, doxycycline therapy reduces *P. gingivalis*-induced inflammatory cytokines and decreases the size of atherosclerotic lesions [173]. After periodontal therapy, subjects exhibit reduced levels of proinflammatory mediators [157,174–179]. For example, Forner *et al.* reported that scaling reduces circulating IL-8, increases circulating IL-6 and has no effect on levels of IL-1β, TNF-α, IL-10 or IL-12p70 [180]. By contrast, full mouth subgingival debridement is reported to reduce levels of TNF-α and other inflammatory mediators, including hsCRP and soluble E-selectin [12,181,182]. A transient increase in IL-6 has also been reported by other investigators, as have transient increases in other inflammatory mediators [183,184]. The effects of periodontal treatment on circulating hsCRP are subject to modulation by confounders, such as obesity [185]. Soluble cell adhesion molecules are elevated in subjects with generalized aggressive periodontitis [33,39], but soluble E-selectin declines when subjects are treated by scaling and root planing [186]. Periodontal therapy also ameliorates subclinical indices of atherosclerosis. Although transient endothelial dysfunction has been reported after subgingival periodontal therapy [187], endothelial cell function generally improves in periodontitis subjects who receive either surgical or nonsurgical treatment [174–176,184,188]. A recent report demonstrates that periodontal therapy significantly reduces IMT of the carotid artery [189], suggesting that treatment reduces atherosclerosis.

Although the majority of studies have focused on inflammatory cytokines, recent work also suggests that periodontal therapy improves dyslipidemia. One report indicates that intensive periodontal therapy reduces total cholesterol and LDL-C but has no effect on HDL-C or TG when tested 6 months following therapy [177]. However, most studies demonstrate favorable changes in both LDL- and HDL-C after periodontal therapy [155,190,191]. Although Losche *et al.* did not observe changes in HDL-C or LDL-C, they reported a decline in LpPLA2 after periodontal therapy [192]. In an extensive study of HDL metabolism, Pussinen *et al.* demonstrated that mechanical periodontal therapy plus antibiotic treatment resulted in increased HDL-C and an increase in the ratio of HDL-2:HDL-3, a shift that should favor reverse cholesterol transport and therefore amelioration of atherosclerosis. This study also showed

increased HDL-associated phospholipids and an increase in the ratio of sphingomyelin/phosphatidylcholine in the HDL particle after periodontal therapy [115]. The changes in HDL composition were attributed to treatment-induced decreases in phospholipid transfer protein and increases in cholesterol ester transfer protein. Importantly, enhanced cholesterol efflux was observed when RAW 264.7 macrophages were cultured with HDL isolated from subjects after periodontal therapy, suggesting an increase in athero-protective reverse cholesterol transport [115]. Periodontal therapy also has a favorable impact on lipid oxidation. Lipid peroxides and anti-malonaldehyde-modified oxLDL decline after scaling and root planing [156,157]. Together, these studies support the concept that periodontal treatment ameliorates dyslipidemia. These findings not only confirm the association between periodontal disease and atherosclerosis, they also suggest periodontal therapy as a potential strategy to control atherosclerosis.

Conclusion

Most studies to date support the concept of an association between periodontal disease and atherosclerosis. Although chronic inflammation clearly plays a role in the pathogenesis of both diseases, alterations in lipoproteins and lipoprotein metabolism appear to be important as well. Although the associations are modest, they appears to be strongest for ApoB-containing lipoproteins. The limited data regarding effects of periodontal treatment of lipoprotein/lipid profiles are also supportive of an association between lipid metabolism, periodontitis and cardiovascular disease. Given the enormous costs associated with the morbidity and mortality that stem from atherosclerosis and cardiovascular disease, these studies highlight the need for mechanistic studies to delineate the mechanisms underlying the correlation between periodontitis and atherosclerosis.

Future perspective

Of particular note are patients with aggressive periodontitis. This disease develops early in life, making it likely that cumulative effects of dyslipidemia and chronic inflammation over many years results in severe atherosclerosis and cardiovascular events in this cohort of patients. Given the recent report of a genetic association between aggressive periodontitis and cardiovascular disease, this would appear to be an important area for future studies.

Interpretation of studies in this area of investigation is complicated by the variety of indices and measures that are used to define periodontal disease or atherosclerosis. As such, there remain inconsistencies in both the quantitative and qualitative relationships between periodontal disease and lipid metabolism. However, a promising strategy is the use of antipathogen antibodies as markers of periodontal disease. As noted above, there is evidence that antipathogen antibodies are more reliable correlates of cardiovascular disease than are clinical measures of periodontitis [141]. The biological specimens needed to measure these antibodies (blood plasma) can be obtained relatively easily and in a noninvasive manner, and it also seems feasible to develop cost-effective high-throughput assays to quantify them. One envisions that screening for such antibodies might be a standard component of the annual physical examination in the future. This strategy would not only facilitate identification of subjects at risk of losing their teeth to periodontal disease, but might also allow for early interventions to prevent or reduce severity of atherosclerosis and cardiovascular disease.

Most studies demonstrate increased plasma LDL-C in subjects with periodontitis [36,105, 106,108,112–114] and periodontal therapy tends to reduce LDL-C. Although the mechanism underlying this response is uncertain, there is evidence to suggest that oral pathogens may augment expression of the rate-limiting enzyme in cholesterol synthesis, HMG-CoA reductase [117]. This enzyme is the target of the highly successful statin drugs. It is not uncommon for

patients at risk for developing cardiovascular disease to be maintained on statins for long periods of time, with only modest deleterious side effects [193,194]. As such, it is tempting to speculate that future periodontitis patients might be maintained on statins in addition to conventional periodontal therapy, in order to reduce their risk of developing cardiovascular disease and other chronic inflammatory diseases.

Although this article has been focused on atherosclerosis and cardiovascular disease, abnormalities in lipoproteins/lipoprotein metabolism are associated with other diseases, such as metabolic syndrome, insulin resistance, Type 2 diabetes mellitus and fatty liver disease [195–199]. Although correlations between periodontal disease and Type 2 diabetes mellitus are well established, it is less clear if periodontitis predisposes subjects to develop other metabolic diseases. Routine screening for antibodies against periodontal pathogens may identify patients at risk for developing these disorders. At the very least, patients with periodontitis should be carefully monitored for signs of Type 2 diabetes mellitus, fatty liver and other metabolic diseases.

Executive summary

Periodontal disease, atherosclerosis & cardiovascular disease

- Most studies indicate a modest association between periodontal and cardiovascular disease.
- Associations tend to be strongest in studies correlating periodontitis with subclinical indices of atherosclerosis.
- Inflammatory mediators, including proinflammatory cytokines and high-sensitivity C-reactive protein, are elevated in periodontitis.

Periodontal disease, lipoproteins & lipoprotein metabolism

- LDL-C and triacyglycerols tend to be elevated in periodontitis. Although there is evidence that HDL levels are low in periodontitis, this outcome is less consistent.
- Lipoprotein particles tend to be smaller, and small, dense LDLs tend to be increased in subjects with aggressive periodontitis. These alterations suggest a shift towards a more atherogenic lipoprotein profile.
- Oral pathogens induce antibodies that crossreact with oxidized LDL. These antibodies may opsonize oxidized LDL and promote its uptake by foam cells.
- Associations between lipoproteins/lipids and periodontal disease are relatively modest. Hence, although these modulations contribute to the pathogenesis of atherosclerosis, it is likely that a multitude of factors (periodontitis-induced changes in lipid metabolism/inflammation and environmental/genetic factors) determine the propensity of an individual to develop atherosclerosis and cardiovascular disease.

Effects of periodontal therapy on lipoproteins & lipoprotein metabolism

- Periodontal therapy reduces circulating inflammatory mediators and also improves subclinical indices of atherosclerosis.
- LDL-C is reduced after periodontal therapy and HDL shifts to favor the HDL-2 subspecies, which may be more anti-atherogenic. In support of this, enhanced cholesterol efflux is observed when macrophages are incubated with HDL isolated after periodontal therapy.

Conclusions

- The evidence to date suggests that periodontal disease may induce changes in lipoprotein metabolism that promote atherosclerosis and that periodontitis patients are at increased risk for developing cardiovascular disease.
- Antibodies against oral pathogens are markers of periodontal disease that can be readily quantified in relatively inexpensive assays. The biological samples required for these assays (peripheral blood) are easily obtained in a noninvasive manner.
- As such, it is feasible for physicians to screen patients for periodontal disease during annual physical examinations. Given the costs, morbidity and mortality associated with cardiovascular disease, this screening could be an effective way to identify individuals who have increased risk for developing these life-threatening diseases.

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Table 1

Properties of lipoprotein species.

Lipoprotein	Density (g/ml)	Diameter (Å)	Apolipoproteins	Composition (% by weight)	
				Triglyceride	*Total cholesterol*
Chylomicron	<0.94	75–1200	A-I, A-II, AIV, AV, B-48, C-I, C-II, C-III and E	80–95	3–6
VLDL-I	<1.006	330–700	B-100, C-I, C-II, C-III and E	45–65	20–30
VLDL-II	1.006–1.010	300–330			
IDL-1	1.008–1.022	285–300	B-100, C-I, C-II, C-III and E	15	47
IDL-2	1.013–1.019	272–285			
LDL-I	1.019–1.023	272–285	B-100	4–8	51–58
LDL-II	1.023–1.034	256–272			
LDL-III	1.034–1.044	242–256			
LDL-IV	1.044–1.06	220–242			
HDL-2	1.063–1.125	88–120	A-I, A-II, A-IV C-I, C-II, C-III, D, E, J, L-I and M	2–7	18–25
HDL-3	1.125–1.210	72–88			