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Atherogenic lipoprotein parameters in patients with aggressive periodontitis

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Background and Objective: Certain types of chronic infection increase the plasma level of very-low-density lipoprotein, leading to formation of the particularly atherogenic low-density lipoprotein subclass, small dense low-density lipoprotein. In the present study, we examined whether aggressive forms of periodontis are associated with these atherogenic lipoprotein parameters.

Material and Methods: Twelve healthy control subjects without periodontitis, 12 subjects with localized aggressive periodontitis and 12 subjects with generalized aggressive periodontitis were studied. Lipoprotein subclass levels were determined using nuclear magnetic resonance methodology.

Results: Healthy control subjects, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects had progressively higher plasma levels of very-low-density lipoprotein and progressively smaller average low-density lipoprotein size ($p < 0.05$, one-way analysis of variance). In pairwise comparisons, differences were only significant between healthy controls and generalized aggressive periodontitis subjects ($p < 0.05$, Tukey's post test). After adjustment for body mass index, the mean periodontal pocket depth correlated positively with plasma very-low-density lipoprotein levels ($p = 0.047$). Very-low-density lipoprotein concentrations correlated positively with small dense low-density lipoprotein levels and negatively with average low-density lipoprotein size. Prevalence of the atherogenic lipoprotein pattern-B in healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects was 8.3%, 33.3% and 66.6%, respectively.

Conclusion: These results indicate that periodontal infection is associated with elevated plasma levels of atherogenic lipoprotein species. This association may account for the increased risk of periodontitis patients for cardiovascular disease.

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Recent studies indicate that severe periodontitis may increase the risk of coronary heart disease and stroke (1–9). Although the molecular mechanism that links these conditions is currently unclear, recent data suggest that plasma lipoproteins are involved (10–15).

A particularly important role may be played by the very-low-density lipoprotein. Previous studies have shown that certain bacterial infections may elevate the plasma concentration of very-low-density lipoprotein in humans (16–18), and, likewise, injection of bacterial lipopolysaccharide has been shown to increase plasma very-low-density lipoprotein levels in rats (19). The immediate result of elevated very-low-density lipoprotein levels may be beneficial: very-low-density lipoprotein binds lipopolysaccharide and

neutralizes the toxic, inflammatory effects of this compound, thus protecting infected organisms against microbe-induced fever, hypotension and death (20). It has therefore been proposed that specific changes in lipoprotein metabolism are part of the innate immune response, providing immediate protection against infection and inflammation (16–18).

While attenuation of lipopolysaccharide toxicity by a temporary increase of plasma very-low-density lipoprotein levels may be beneficial, chronic elevation of very-low-density lipoprotein is atherogenic (21–23). Current models suggest that elevated plasma concentrations of very-low-density lipoprotein increase the exchange of neutral lipids between very-low-density lipoprotein and the low-density lipoprotein, a process that is mediated by the plasma cholesteryl ester transfer protein (22). The result of this enhanced exchange is an increased triglyceride and decreased cholesteryl ester content of the low-density lipoprotein core. Subsequent hydrolysis of low-density lipoprotein-associated triglycerides by hepatic lipase is thought to generate low-density lipoprotein particles that, in general, are smaller and denser than low-density lipoprotein particles from subjects with normal very-low-density lipoprotein levels.

Many studies have indicated that small, dense low-density lipoprotein is particularly atherogenic (21–23). Four distinct properties are thought to contribute to this increased atherogenicity.

(i) Small dense low-density lipoprotein has a lower affinity for the apoB/E receptor than larger low-density lipoprotein (24–27); this delays metabolic clearing of small dense low-density lipoprotein from the circulation and, as a result, increases the likelihood that the lipoprotein particle will participate in atherogenic events.

(ii) Small dense low-density lipoprotein penetrates the vascular wall more easily than larger low-density lipoprotein (28); this increases the chance of atherogenic lipoprotein modification in the intima.

(iii) Small dense low-density lipoprotein has a higher affinity for vascular glycosaminoglycans than larger low-density lipoprotein (29); this prolongs the residence time of small dense low-density lipoprotein in the intima and, as a result, increases exposure of the lipoprotein particle to modification.

(iv) Small dense low-density lipoprotein is more susceptible to oxidation than larger low-density lipoprotein (30–34); this may increase the amount of atherogenic oxidation products that are generated upon exposure of low-density lipoprotein to reactive oxygen species in the vascular wall.

The total collection of circulating low-density lipoprotein particles in any subject contains several subclasses of particles that differ in size and density. The low-density lipoprotein profile in which small dense low-density lipoprotein particles predominate has been designated 'pattern-B', whereas a normal low-density lipoprotein profile, with mostly larger low-density lipoprotein, is referred to as 'pattern-A'. Many studies have shown that subjects with a pattern-B lipoprotein profile have a three- to sevenfold higher risk of cardiovascular events than subjects with a pattern-A profile (21–23).

As certain types of chronic infection and inflammation elevate circulating very-low-density lipoprotein and small dense low-density lipoprotein levels (16–18), we hypothesized that periodontal infection is also associated with these atherogenic lipoprotein parameters. Our analysis of 24 patients with aggressive periodontitis and of 12 control subjects without periodontitis shows that mean periodontal pocket depth indeed correlates positively with the plasma level of very-low-density lipoprotein, and that very-low-density lipoprotein levels in these subjects correlate positively with circulating concentrations of small dense low-density lipoprotein. These results suggest that the previously observed increase in risk of periodontitis patients for coronary heart disease or stroke (1–9) is linked to atherogenic lipoprotein parameters.

Material and methods

Human subjects

The present study was conducted with 12 healthy control subjects without periodontitis, 12 subjects with localized aggressive periodontitis and 12 subjects with generalized aggressive periodontitis. Gender, race and age distribution of healthy controls and aggressive periodontitis subjects were as shown in Table 1. All subjects were nonhypertensive and had no reported history of diabetes. No subjects used oral contraceptives, lipid-lowering drugs, or other medication. Healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects were identified at the Clinical Research Center for Periodontal Diseases at Virginia Commonwealth University (Richmond, VA, USA). Each subject received a complete periodontal evaluation that included assessment of pocket depth, attachment loss, bleeding index, gingival index and plaque index (35). Measurements were performed at four sites per tooth (mesiobuccal, midbuccal, distobuccal and midlingual). Clinical examinations were performed by three dentists who were calibrated to provide uniform measures (36,37). To qualify as a localized aggressive periodontitis subject, patients needed to have at least 4 mm attachment loss on at least two permanent first molars and incisors (at least one molar needed to be affected) and to have no more than two teeth (which were not first molars or incisors) that were affected by ≥ 5 mm attachment loss. To qualify as a generalized aggressive periodontitis subject, patients needed to have at least eight teeth affected by ≥ 5 mm attachment loss, at least three of which were not first molars or incisors. Initial diagnosis of localized aggressive periodontitis or generalized aggressive periodontitis was established after puberty and before the subject's 31st birthday. The study was approved by the Institutional Review Board of Vir-

Table 1. Biographic data and periodontal parameters of healthy control subjects, subjects with localized aggressive periodontitis and subjects with generalized aggressive periodontitis

	Healthy control subjects[a] ($n = 12$)	LAgP subjects[a] ($n = 12$)	GAgP subjects[a] ($n = 12$)	One-way analysis of variance
Gender (female/male)	6/6	10/2	6/6	NA
Race (African–American/Caucasian)	11/1	12/0	11/1	NA
Age (years, mean ± SEM)	34.1 ± 2.6	34.0 ± 2.3	41.7 ± 1.7	$p = 0.030$
Body mass index (mean ± SEM)[b]	27.1 ± 1.6	26.1 ± 1.9	33.0 ± 2.2	$p = 0.037$
Mean pocket depth (mm ± SEM)	2.0 ± 0.6	2.5 ± 0.1	3.4 ± 0.8	$p < 0.0001$
Mean attachment loss (mm ± SEM)	0.0 ± 0.0	0.8 ± 0.2	3.1 ± 0.6	$p < 0.0001$
Mean bleeding index ± SEM	0.2 ± 0.0	0.4 ± 0.1	0.6 ± 0.1	$p = 0.0002$
Mean gingival index ± SEM	0.7 ± 0.1	1.2 ± 0.1	1.6 ± 0.1	$p < 0.0001$
Mean plaque index ± SEM	0.4 ± 0.1	0.7 ± 0.1	1.3 ± 0.1	$p < 0.0001$

Of the 24 subjects with aggressive periodontitis, 12 had received no treatment within 1 year of the sample date, whereas 12 had received varying degrees of limited treatment. Most of the subjects (31 out of 36) were nonsmokers; three were former smokers and two were current smokers. *p*-values for one-way analysis of variance group comparisons are shown.

[a]Healthy control and generalized aggressive periodontitis data are from the same subjects, as described in Rufail *et al.* (15).

[b]Body mass index data were available from nine healthy control subjects without periodontitis, from 10 subjects with localized aggressive periodontitis and from 11 subjects with generalized aggressive periodontitis.

GAgP, generalized aggressive periodontitis; LAgP, localized aggressive periodontitis; NA, not applicable.

ginia Commonwealth University, and all subjects participated after giving informed consent.

Lipoprotein subclass analysis

Lipoprotein particle concentrations and size were measured in total plasma samples by proton nuclear magnetic resonance spectroscopy (LipoScience, Inc., Raleigh, NC, USA) (38,39). The following lipoprotein subclasses were distinguished: large very-low-density lipoprotein (> 60 nm), medium-sized very-low-density lipoprotein (35–60 nm), small very-low-density lipoprotein (27–35 nm), intermediate-density lipoprotein (23–27 nm), large low-density lipoprotein (21.2–23 nm), small low-density lipoprotein (18–21.2 nm), large high-density lipoprotein (8.8–13 nm), medium-sized high-density lipoprotein (8.2–8.8 nm) and small high-density lipoprotein (7.3–8.2 nm). Plasma concentrations of triglycerides, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were derived from nuclear magnetic resonance analyses by assuming that the particles contain normal amounts of cholesterol and triglycerides. Previous studies have shown that these derived plasma concentrations correlate well with standard laboratory tests (38).

Statistical analyses

Periodontal parameters and lipoprotein subclasses were compared among the three groups of subjects using one-way analysis of variance with Tukey's post test. Correlations between different parameters were assessed using multiple regression analysis. Statistical analyses were performed using GRAPHPAD PRISM (GraphPad Prism, San Diego, CA, USA) and JMP (version 6.0.2; SAS Institute Inc., Cary, NC, USA) software. In all analyses, statistical significance was declared at the 5% level.

Results

Periodontal parameters

The mean values for periodontal pocket depth, attachment loss, bleeding index, gingival index and plaque index are reported in Table 1 and are characteristic of the diagnostic categories.

Lipoprotein subclass profiles

To determine if differences between the three subject groups in the degree of periodontal infection and inflammation correspond with differences in specific lipoprotein subclasses, we assessed the average lipoprotein profiles of the three groups. Table 2 shows that medium-sized very-low-density lipoprotein, total very-low-density lipoprotein and total intermediate-density lipoprotein concentrations were progressively higher in healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects (i.e. plasma levels were higher in localized aggressive periodontitis subjects than in healthy control subjects without periodontitis, and higher in generalized aggressive periodontitis subjects than in localized aggressive periodontitis subjects) ($p < 0.05$, one-way analysis of variance). The average low-density lipoprotein size was progressively smaller in healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects ($p < 0.05$, one-way analysis of variance). In pairwise comparisons using Tukey's post test, differences were only significant between healthy controls and generalized aggressive periodontitis subjects ($p < 0.05$). No differences among the three groups of subjects were observed in any of the three high-density lipoprotein subclasses (Table 2).

Correlations between periodontal parameters and very-low-density lipoprotein

To assess whether the severity of periodontal infection (Table 1) correlates with plasma very-low-density lipoprotein levels (Table 2), we plotted periodontal parameters and plasma very-low-density lipoprotein levels, as shown in Fig. 1. Within the total group of healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects, plasma concentrations of very-low-density lipoprotein correlated positively with mean periodontal pocket depth ($p = 0.008$, $r = 0.44$) and with

Table 2. Plasma lipoprotein parameters and plasma lipid values of healthy control subjects, subjects with localized aggressive periodontitis and subjects with generalized aggressive periodontitis

	Healthy control subjects[a] ($n = 12$)	LAgP subjects ($n = 12$)	GAgP subjects[a] ($n = 12$)	One-way analysis of variance
Large very-low-density lipoprotein (nmol/L)	1.1 ± 0.5	1.0 ± 0.3	3.5 ± 1.3	$p = 0.065$
Medium very-low-density lipoprotein (nmol/L)	9.4 ± 1.7	13.2 ± 3.0	24.6 ± 5.9[b]	**$p = 0.028$**
Small very-low-density lipoprotein (nmol/L)	24.5 ± 5.4	25.6 ± 3.9	35.0 ± 5.3	**$p = 0.268$**
Total very-low-density lipoprotein (nmol/L)	35.0 ± 6.7	39.8 ± 6.9	63.1 ± 9.6[b]	**$p = 0.036$**
Average very-low-density lipoprotein size (nm)	57.4 ± 4.0	51.2 ± 2.5	54.4 ± 2.6	$p = 0.394$
Intermediate-density lipoprotein (nmol/l)	25 ± 12	40 ± 18	87 ± 17[b]	**$p = 0.020$**
Large low-density lipoprotein (nmol/L)	448 ± 49	331 ± 50	316 ± 59	$p = 0.171$
Small low-density lipoprotein (nmol/L)	488 ± 104	721 ± 153	947 ± 152[c]	$p = 0.078$
Total low-density lipoprotein (nmol/L)	961 ± 105	1093 ± 149	1349 ± 133	$p = 0.117$
Average low-density lipoprotein size (nm)	21.4 ± 0.2	21.0 ± 0.3	20.6 ± 0.3[b]	**$p = 0.047$**
Large high-density lipoprotein (μmol/L)	8.6 ± 0.9	7.5 ± 0.8	6.7 ± 1.1	$p = 0.383$
Medium high-density lipoprotein (μmol/L)	3.5 ± 1.5	1.4 ± 0.5	4.4 ± 1.4	$p = 0.229$
Small high-density lipoprotein (μmol/L)	18.4 ± 2.2	19.3 ± 1.7	22.9 ± 1.9	$p = 0.231$
Total high-density lipoprotein (μmol/L)	30.5 ± 1.3	28.1 ± 1.5	34.0 ± 2.5	$p = 0.089$
Average high-density lipoprotein size (nm)	9.1 ± 0.1	9.1 ± 0.2	8.9 ± 0.1	$p = 0.323$
Low-density lipoprotein cholesterol (mg/dL)	93 ± 8	92 ± 9	110 ± 8	$p = 0.250$
High-density lipoprotein cholesterol (mg/dL)	51 ± 3	46 ± 2	50 ± 5	$p = 0.552$
Total cholesterol (mg/dL)	154 ± 9	149 ± 10	179 ± 7	**$p = 0.045$**
Total triglycerides (mg/dL)	70 ± 9	73 ± 11	126 ± 19[b,d]	**$p = 0.010$**

Lipid values were derived from lipoprotein subclass distributions, assuming normal lipid content of the lipoprotein particles.
p-values in bold indicate statistical significance.
[a]Healthy control and generalized aggressive periodontitis data are from the same subjects as described in Rufail *et al.* (15).
[b]$p < 0.05$ in comparison with healthy control subjects without periodontitis (one-way analysis of variance with Tukey post test).
[c]$p < 0.05$ in comparison with healthy control subjects without periodontitis (Student's *t*-test).
[d]$p < 0.05$ in comparison with subjects with localized aggressive periodontitis (one-way analysis of variance with Tukey post test).
GAgP, generalized aggressive periodontitis; LAgP, localized aggressive periodontitis.

mean attachment loss ($p = 0.005$, $r = 0.46$). Correlations remained significant when the mean values of healthy control subjects (the stars in Fig. 1A,B) were excluded from the analyses ($p = 0.040$, $r = 0.42$; and $p = 0.035$, $r = 0.43$, respectively).

As plasma very-low-density lipoprotein levels may be elevated in subjects who are overweight (body mass index = 25–30) or obese (body mass index > 30), we assessed the possible influence of body mass index on the data. Within the total group of healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects, body mass index correlated positively with plasma very-low-density lipoprotein levels ($p = 0.002$, $r = 0.56$), but no significant correlation existed between body mass index and mean pocket depth ($p = 0.356$, $r = 0.03$), or between body mass index and mean attachment loss ($p = 0.181$, $r = 0.25$). Upon multiple regression analysis to adjust for body mass index, the correlation between mean periodontal pocket depth and plasma very-low-density lipoprotein concentration remained significant ($p = 0.047$). After adjustment for body mass index, the correlation between mean attachment loss and very-low-density lipoprotein concentration lost significance, but continued to indicate a positive trend ($p = 0.056$).

In multiple regression analysis, age did not correlate with plasma very-low-density lipoprotein levels. No statistically significant correlations were observed between the bleeding index, gingival index, or plaque index and the plasma concentration of very-low-density lipoprotein.

Very-low-density lipoprotein, small dense low-density lipoprotein and average low-density lipoprotein size

Studies have indicated that elevated plasma concentrations of very-low-density lipoprotein may lead to formation of the atherogenic low-density lipoprotein subclass, small dense low-density lipoprotein (22). In the present group of localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects, plasma very-low-density lipoprotein levels correlated positively with circulating small dense low-density lipoprotein concentrations (Fig. 2A) and negatively with average low-density lipoprotein size (Fig. 2B).

Figure 2C shows that healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects had progressively higher plasma levels of small dense low-density lipoprotein and progressively lower plasma levels of large low-density lipoprotein. Separately, differences in the plasma levels of small dense low-density lipoprotein and large low-density lipoprotein were not statistically significant ($p > 0.05$, one-way analysis of variance); however, differences in the plasma levels of small dense low-density lipoprotein and large low-density lipoprotein jointly resulted

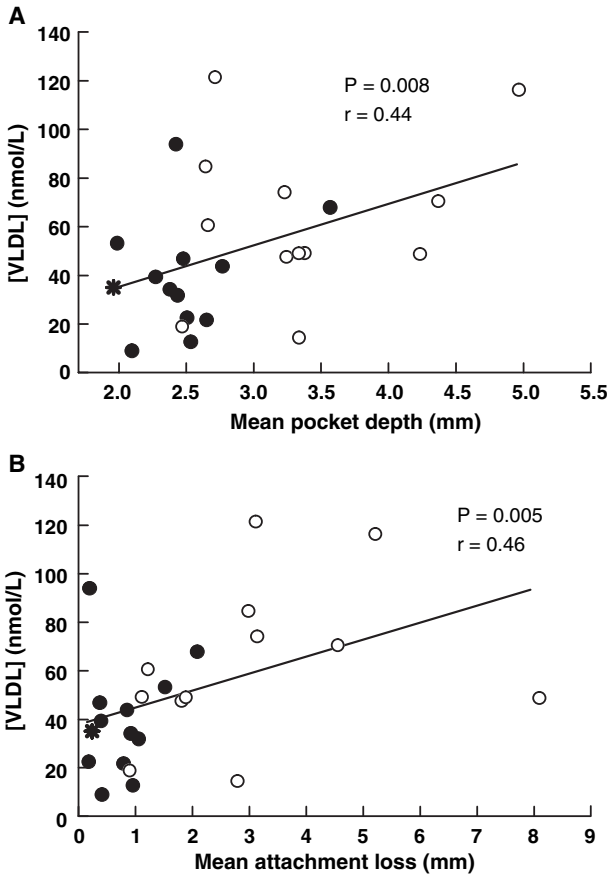

Fig. 1. Correlations between periodontal parameters and the plasma concentration of very-low-density lipoprotein. (A) Correlation between mean pocket depth and plasma very-low-density lipoprotein levels. (B) Correlation between mean attachment loss and plasma very-low-density lipoprotein levels. Black circles, subjects with localized aggressive periodontitis; white circles, subjects with generalized aggressive periodontitis; stars, average values of healthy control subjects without periodontitis ($n = 12$). VLDL, very-low-density lipoprotein.

in significantly different average low-density lipoprotein sizes in healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects ($p < 0.05$, one-way analysis of variance) (Fig. 2D). In pairwise comparisons of the three subject groups, differences in average low-density lipoprotein size were only significant between healthy controls and generalized aggressive periodontitis subjects ($p < 0.05$, Tukey post test).

Pattern-A and pattern-B lipoprotein profiles

Average low-density lipoprotein size defines whether a subject has a pattern-A (> 20.5 nm) or a pattern-B (≤ 20.5 nm) lipoprotein profile. In the present study, 8.3% of the healthy control subjects without periodontitis (1 out of 12), 33.3% of the localized aggressive periodontitis subjects (4 out of 12) and 66.6% of the generalized aggressive periodontitis subjects (8 out of 12) had a pattern-B lipoprotein profile. The higher prevalence of pattern-B in the localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects, occurred while average plasma concentrations of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol in the three groups were essentially the same (Table 2). Total plasma cholesterol and total plasma triglyceride levels were moderately elevated in generalized aggressive periodontitis subjects, but average concentrations were well below hypercholesterolemic or hypertriglyceridemic levels (Table 2).

Discussion

The present study identifies correlations between mean pocket depth, mean attachment loss and the plasma concentration of very-low-density lipoprotein. Previous studies have shown that elevated very-low-density lipoprotein levels enhance the cholesteryl ester transfer protein-mediated exchange of neutral lipids between very-low-density lipoprotein and low-density lipoprotein, leading to an increased triglyceride and decreased cholesteryl ester content of the low-density lipoprotein core (22). Subsequent hydrolysis of low-density lipoprotein-associated triglycerides by hepatic lipase generates small dense low-density lipoprotein particles that are particularly atherogenic (24–34,40). Subjects who have predominantly small dense low-density lipoprotein in their blood (i.e. subjects with a pattern-B lipoprotein profile) have a three- to sevenfold increased risk of cardiovascular events (21–23).

Consistent with current models of small dense low-density lipoprotein formation (22), we found a strong correlation between the plasma levels of very-low-density lipoprotein and small dense low-density lipoprotein in localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects (Fig. 2A,B). Furthermore, very-low-density lipoprotein and small dense low-density lipoprotein levels were progressively higher (Table 2, Fig. 2C), average low-density lipoprotein size was progressively smaller (Fig. 2D) and the pattern-B lipoprotein profile was progressively more prevalent in healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects. Our results therefore suggest that the increased risk of periodontitis patients for heart disease and stroke (1–7) may be a result, in part, of an increased occurrence of lipoprotein pattern-B among periodontitis patients.

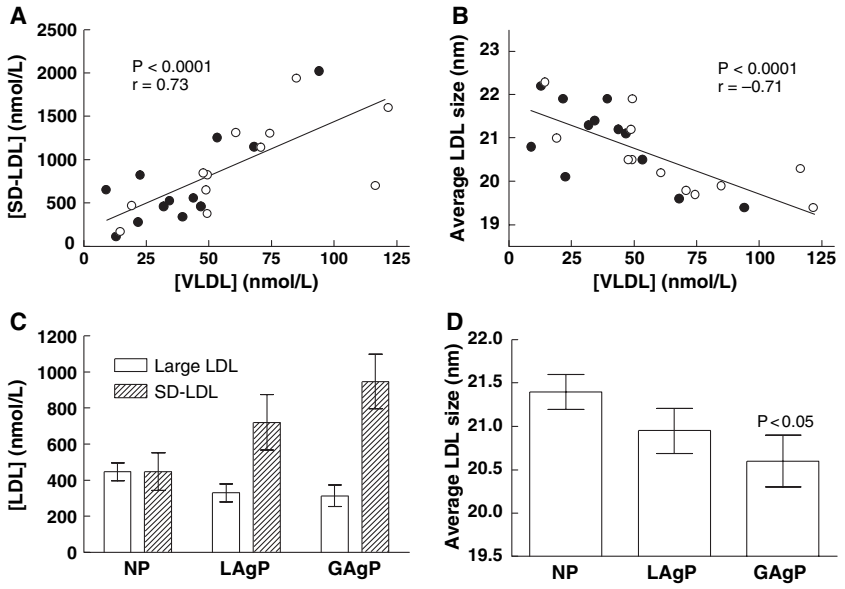

Fig. 2. Very-low-density lipoprotein and small dense low-density lipoprotein parameters in healthy controls, subjects with localized aggressive periodontitis and subjects with generalized aggressive periodontitis. (A) Correlation between the plasma concentrations of very-low-density lipoprotein and small dense low-density lipoprotein in subjects with localized aggressive periodontitis (black circles) and generalized aggressive periodontitis (white circles). (B) Correlation between the plasma concentration of very-low-density lipoprotein and average low-density lipoprotein size in subjects with localized aggressive periodontitis (black circles) and generalized aggressive periodontitis (white circles). (C) Distribution of large low-density lipoprotein and small dense low-density lipoprotein subclasses. Note that the small dense low-density lipoprotein levels of healthy controls, localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects were not significantly different in a one-way analysis of variance using the Tukey post test ($p > 0.05$); however, the small dense low-density lipoprotein levels of healthy controls and generalized aggressive periodontitis subjects were significantly different in a Student's *t*-test ($p < 0.05$); see also Rufail *et al.* (15). (D) Average low-density lipoprotein size. The *p*-value refers to comparison with healthy control subjects, without periodontitis, in a one-way analysis of variance with Tukey's post test. GAgP, subjects with generalized aggressive periodontitis; LDL, low-density lipoprotein; LAgP, subjects with localized aggressive periodontitis; NP, no periodontitis (i.e. healthy control subjects); SD-LDL, small dense low-density lipoprotein; VLDL, very-low-density lipoprotein.

Consistent with established features of the pattern-B lipoprotein profile, plasma triglyceride and cholesterol levels of localized aggressive periodontitis subjects and generalized aggressive periodontitis subjects were mostly within the normal range (Table 2). Conversion of large low-density lipoprotein to small dense low-density lipoprotein is known to increase sharply when plasma triglyceride levels reach $\sim$130 mg/dL (1.5 mmol/L) (22), which is well below the plasma level that defines hypertriglyceridemia (i.e. $\geq$200 mg/dL). In addition, pattern-B is known to occur in the absence of alarmingly high low-density lipoprotein-cholesterol levels (22,23). This means that the increased risk of periodontitis patients for heart disease and stroke may not be obvious from conventional lipid measurements. While plasma triglyceride levels approaching 130 mg/dL may suggest the possible presence of a pattern-B lipoprotein profile, a more complete risk assessment requires comprehensive lipoprotein subclass analysis (22,23).

The observation that, after adjustment for body mass index, mean pocket depth correlates positively with circulating concentrations of very-low-density lipoprotein, supports the notion that periodontal infection may result in the pattern-B lipoprotein profile. Although our results do not demonstrate this causality, previous studies have shown that certain types of infection and inflammation may increase plasma triglyceride levels and lead to the formation of lipoprotein pattern-B in humans (16–18). In addition, experimental injection with lipopolysaccharide has been shown to increase plasma triglyceride levels in animals: low doses of lipopolysaccharide increased secretion of triglyceride-rich very-low-density lipoprotein into the circulation, whereas high doses decreased very-low-density lipoprotein catabolism (19). Periodontal infections, which involve access of gram-negative bacteria, such as *Porphyromonas gingivalis*, to the bloodstream, may affect plasma very-low-density lipoprotein levels in similar ways. As periodontal infections are chronic, elevation of plasma very-low-density lipoprotein may also be chronic, which, in turn, may lead to the establishment of a pattern-B lipoprotein profile and an associated increase in cardiovascular risk.

It should be noted that elevated plasma levels of very-low-density lipoprotein and small dense low-density lipoprotein also occur in diabetes (41–43), and previous studies have indicated that diabetic patients with poor glycemic control are at an increased risk of developing periodontitis (12,44,45). Although the subjects with localized aggressive periodontitis and generalized aggressive periodontitis in the present study have no reported history of diabetes, it is possible that the early onset of this disease in some patients may have affected very-low-density lipoprotein and small dense low-density lipoprotein levels. However, localized aggressive periodontitis and generalized aggressive periodontitis both have a distinct inheritable component (37) and typically develop early in life in the absence of diabetes. Furthermore, animal studies involving experimentally induced periodontitis in the absence of diabetes (8,9) indicate that infection with oral bacteria alone is atherogenic and may account for increased cardiovascular risk.

In summary, the present study identifies an association between

aggressive periodontitis and atherogenic lipoprotein subclasses in a predominantly African–American group of subjects. This association is consistent with the notion that infection-induced lipoprotein changes may elevate the risk of periodontitis patients for heart disease and stroke.

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