LDL Hypercholesterolemia Is Associated With Accumulation of Oxidized LDL, Atherosclerotic Plaque Growth, and Compensatory Vessel Enlargement in Coronary Arteries of Miniature Pigs

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Abstract—The association between accumulation of oxidized low density lipoprotein (LDL) and (1) progression of atherosclerotic plaques and (2) compensatory enlargement was assessed in the coronary arteries of LDL-hypercholesterolemic miniature pigs. In miniature pigs fed a 4% cholesterol diet, LDL cholesterol levels increased from 27±3.5 mg/dL (mean±SEM, n=36) to 250±28 mg/dL (n=10), 260±15 mg/dL (n=6), and 260±17 mg/dL (n=10) at 6, 14, and 24 weeks, respectively. Mean intimal areas of lesions in the left anterior descending coronary artery of hypercholesterolemic pigs were 0.16±0.046 mm² at 6 weeks (n=10) and increased 5.4-fold (n=6, P<.05) and 10.6-fold (n=10, P<.001) at 14 and 24 weeks, respectively. Plaque growth was associated with an increase in mean internal elastic lamina area, from 1.44±0.17 to 4.38±0.52 mm² (P=.007) and in mean luminal area from 1.42±0.15 mm² in control pigs to 4.38±0.52 mm² in pigs fed a cholesterol diet for 24 weeks (P=.007 vs control). Levels of total LDL in the intima, measured immunocytochemically, were 0.031±0.0098, 0.11±0.057 (P=.05), and 0.43±0.082 U (P<.001) at 6, 14, and 24 weeks, respectively. Corresponding levels of oxidized LDL were 0.034±0.023, 0.11±0.050 (P<.05), and 0.44±0.065 U (P<.001), respectively, suggesting that virtually all LDL in the intima is oxidized. Levels of oxidized LDL in the lesions were correlated with the intimal areas (r=.85, P<.0001) but were independent of plasma levels of LDL cholesterol and of oxidized LDL. Plaque levels of oxidized LDL were also correlated with internal elastic lamina areas (r=.72, P<.0001) and with luminal areas (r=.50, P=.0098). Plaque growth in the coronary arteries of LDL-hypercholesterolemic miniature pigs is associated with (1) an increase in plaque levels of oxidized LDL at constant plasma levels of LDL cholesterol and of oxidized LDL and (2) compensatory vessel enlargement proportional to plaque levels of oxidized LDL. (Arterioscler Thromb Vasc Biol. 1998;18:415-422.)

Key Words: coronary atherosclerosis ■ oxidized LDL ■ plaque growth ■ remodeling

Elevated levels of serum LDL cholesterol are an important risk factor in atherogenesis.1−3 The finding that premature atherosclerosis develops in animals and humans with deficiencies in functional LDL receptors has suggested that there exist alternative pathways for LDL uptake. LDL undergoes oxidative modification when incubated in vitro with endothelial cells, SMCs, or macrophages or when exposed to Cu²⁺.4,5 Oxidized LDLs are rapidly taken up by monocytes/macrophages via scavenger receptors, a process that transforms them into foam cells, which are essential components of fatty streaks and fibrofatty plaques. Accumulation of foam cells in the subendothelial space constitutes an early event in atherosclerosis.4,6 In the present study, a large fraction of the plasma cholesterol in cholesterol-fed miniature pigs was found to be present in LDL, suggesting that cholesterol-fed miniature pigs may represent a suitable model to study the role of LDL and oxidized LDL in the progression of atherosclerosis.

To preserve the luminal area, human coronary arteries may undergo positive remodeling, ie, compensatory enlargement in response to plaque accumulation, as evidenced by the positive correlation (in cross section) between the area encompassed by the IEL and plaque area7−11 or between luminal area and plaque area.12 Mouse and rabbit models have contributed to our understanding of intimal hyperplasia, but they have failed to demonstrate remodeling in response to progressive atherosclerosis in the absence of angioplasty-induced overstretch injury and/or endothelial denudation. Arterial remodeling has been demonstrated not only in humans but also in nonhuman primates.13 In these animals, induction of atherosclerosis in the absence of mechanical injury required between 20 and 36 months of cholesterol feeding.13,14 and although the traditional relationships between plasma lipid levels and intimal area were confirmed, plasma lipid levels did not account for the variability in lumen size.12 The present study demonstrates that in the
absence of mechanical stress, LDL hypercholesterolemia is associated with plaque growth in the coronary arteries of miniature pigs and that plaque growth is associated with compensatory vessel enlargement, or positive remodeling. The aims of the present study therefore were to investigate the correlation between plaque levels of oxidized LDL, as quantified by an mAb specific for oxidatively modified, lipid-associated apoB-100,15,16 and (1) plaque growth and (2) compensatory vessel enlargement in atherosclerotic coronary arteries of hypercholesterolemic miniature pigs.

Methods

Animals

Three-month-old Charles River Laboratories (Cléons, France) miniature pigs (body weight, 28±1.2 kg; mean±SEM of 26 pigs) were housed in a temperature-controlled room (to 20±1°C) at 50±2% humidity on a 12-hour/12-hour light/dark cycle. Atherosclerosis was induced by feeding the animals a diet containing 4% cholesterol, 14% beef tallow, and 1% hog bile extract in daily amounts of 1000 g. Water was provided ad libitum. All experimental procedures for these animals were performed in accordance with protocols approved by the Institutional Animal Care and Research Advisory Committee.

Blood Sampling

Venous blood samples from pigs were collected in 0.1 vol of 0.1 mol/L citrate containing 1 mmol/L EDTA, 20 μmol/L vitamin E, 10 μmol/L BHT, 20 μmol/L dipyridamole, and 15 mmol/L theophylline to prevent in vitro LDL oxidation and platelet activation. Blood samples were centrifuged at 3000 g for 15 minutes at room temperature within 1 hour of collection and stored at −20°C until the assays were performed.

Cardiac Catheterization

Immediately prior to sacrifice the animals were sedated with 1 mL azaperone IM (Stresnil 40 mg/mL, Janssen Pharmaceutica) and premedicated with 7 mg/kg ketamine IM (Imalgene 100 mg/mL, Janssen). The animals were intubated and artificially ventilated with a combination of 70% nitrogen, 14% oxygen, 6% carbon dioxide, and 1% halothane (Fluothane, Pfizer). The hematocrit of each animal was adjusted to 25% to maintain a mean arterial blood pressure of 80 mmHg. The animals were anesthetized as described above, and after thoracotomy their hearts were removed and cannulas inserted into the ascending aorta. The aorta was dissected free of the heart and cut into 7-μm sections. These sections were stained with hematoxylin and eosin and eventually immunostained as described below. Sixty to 80 sections for a distance of 84 μm were analyzed for each artery and mean values were calculated. The length of the analyzed segments thus ranged between 5 and 7 mm. Morphometric parameters of atherosclerotic lesions were measured by planimetry using the 2 Quantiimat color image analyzer (Leica). The external elastic lamina, IEL, medial, intimal, and luminal areas were measured.

Oxidized apoB-100–containing lipoproteins in arterial sections were detected with the specific mAb 4E6.15,16 Sections were developed with alkaline phosphatase–conjugated rabbit-anti-mouse IgG antibodies and the fuchsin/alkaline phosphatase substrate system (Dako). Absorbance was measured in the color image analyzer and the results expressed as mean color intensities.16 Both native and oxidized apoB-100–containing lipoproteins were detected with the specific mAb 13F6, and sections were developed in parallel. mAb 4E6 and mAb 13F6 were used at a final concentration of 5 μg/mL each.

Immunostaining of monocytes/macrophages or SMCs was performed with either the murine mAb 74–22–15 against porcine monocytes/macrophages,17 a generous gift of Dr M.B. Pensert (Laboratory of Veterinary Virology, University of Gent, Gent, Belgium), or with a cross-reacting murine mAb against human smooth muscle α-actin (clone 1A4, Sigma Chemical Co), alkaline phosphatase–conjugated rabbit-anti-mouse IgG antibodies, and the fuchsin/alkaline phosphatase substrate system (Dako). Proliferating cells were immunostained with the monoclonal mouse anti-PCNA (clone PC10, Dakopatts).

Measurement of Plasma Cholesterol Levels and of Oxidized LDL

Plasma total cholesterol levels were determined by using a standard enzymatic colorimetric assay (Boehringer Mannheim). To investigate alterations in cholesterol levels of different lipoprotein components, lipoprotein particles were separated by fast protein liquid chromatography.26,28 Porcine plasma (200 μL) was applied to a Superdex 200HR column and then eluted at 0.5 mL/min with PBS containing 1 mmol/L EDTA (pH 7.5). Fractions were collected (1 minute, 0.5 mL) and cholesterol levels determined by high-performance liquid chromatography. Plasma levels of oxidized LDL were measured in an mAb 4E6–based ELISA as described previously.15,16

Lipoproteins: Preparation and Modification

Lipoproteins isolated by gel filtration were sterilized by filtration through a 0.45-μm low-protein–binding filter (Milllex, Millipore Corp) and stored at 4°C under N2. Copper–oxidized LDL and HDL were prepared by incubation with CuCl2 (final concentration, 640 μg/mL for 16 hours) as described elsewhere,19 and the extent of lysine substitution was determined by measurement of thiobarbituric acid–reactive substances.27

Statistical Analysis

All data were expressed as mean±SEM. All data were analyzed by ANOVA. If the F test was significant, differences between subsets were evaluated by the Mann–Whitney U test performed on logarithmically transformed data using the V2.05a Instat (Graph Pad Software) statistical program. Values of *P<.05 were considered statistically significant. Spearman correlation coefficients were calculated for logarithmically transformed data.

Results

Plasma Levels of Cholesterol and of Oxidized LDL

Fig 1 illustrates the lipoprotein distribution profiles of the pigs before (prediet baseline) and during cholesterol-rich feeding.
LDL and HDL fractions were separated by gel filtration, and their cholesterol levels were measured in isolated fractions by high-performance liquid chromatography. Prediet baseline values in the 26 pigs were 53±3.1 mg/dL (mean±SEM, n=26) for total cholesterol, 27±3.5 mg/dL for LDL cholesterol, and 26±2.2 mg/dL for HDL cholesterol (the Table). Cholesterol levels did not increase further between 6 and 24 weeks of feeding the atherogenic diet. Triglyceride levels also did not change significantly in pigs on the atherogenic diet (the Table). Prediet baseline plasma levels of oxidized LDL were 0.088±0.032 mg/dL (n=26) compared with 0.104±0.0052 mg/dL (n=10) in pigs that were fed the cholesterol-rich diet for as long as 6 months.

Histomorphometric and Immunohistochemical Analyses of Lesions in the LAD

Feeding of the pigs with normal chow for as long as 9 months did not produce intima formation in the LADs, whereas feeding of the atherogenic diet induced plaque formation in the coronary arteries that was associated with accumulation of oxidized LDL. Fig 2 illustrates the accumulation of oxidized LDL, immunostained with the mAb 4E6, in a fatty streak at 14 weeks (Fig 2a and 2b). Oxidized LDL was detected in association with monocytes/macrophages that were immunostained with anti-PCNA antibodies specific for proliferating cells (data not shown). At 14 weeks of cholesterol feeding, fibrofatty plaques had developed (not shown), whereas at 24 weeks atheromatous plaques had developed with proliferating monocytes/macrophages in the oxidized LDL–containing core (Fig 2c and 2d) and with SMCs in the fibrous cap (Fig 2e). The latter cells were not associated with oxidized LDL and were not immunostained with anti-PCNA antibodies (not shown).

Mean IEL areas, ie, areas comprising the lumen and the plaques, of the LADs were 1.44±0.17 mm² (n=10), 1.56±0.16 mm² (n=10, P=NS), 3.15±0.91 mm² (n=6, P=.022), and 4.38±0.52 mm² (n=10, P=.0002) at 0, 6, 14, and 24 weeks, respectively (Fig 3, lower left panel). No lesions were detected in the arteries of normal chow–fed miniature pigs. The mean intimal area was 0.16±0.046 mm² (n=10) at 6 weeks and increased by 5.4-fold (n=6) at 14 weeks and by 10.6-fold (n=10) at 24 weeks (Fig 3). Mean intimal areas of coronary lesions comprising monocytes/macrophages in the oxidized LDL–containing core (Fig 2c and 2d) and with SMCs in the fibrous cap (Fig 2e). The latter cells were not associated with oxidized LDL and were not immunostained with anti-PCNA antibodies (not shown).

| Plasma Cholesterol and Triglyceride Levels in Miniature Pigs That Were Fed the Atherogenic Diet for 6 Weeks |
|---------------------------------------------------|-----------------|----------------|----------------|----------------|
|                      | Total Cholesterol | LDL Cholesterol | HDL Cholesterol | Triglycerides |
| Baseline (n=36)      | 53±3.1           | 27±3.5          | 26±2.2          | 41±4.1        |
| On atherogenic diet (n=26) | 310±16*       | 250±28*         | 74±3.6*         | 45±5.2        |

Data represent mean±SEM and are in milligrams per deciliter.
*P<.001 as determined by Mann-Whitney U test on logarithmically transformed data.
Riphages, representing the cores of the lesions, were 0.16±0.046 mm² at 6 weeks, 0.73±0.20 mm² at 14 weeks, and 1.12±0.14 mm² at 24 weeks. No SMCs were immunostained in the intima at 6 weeks. Mean intimal areas of coronary lesions comprising SMCs, representing the fibrous cap of the lesions, were 0.13±0.059 mm² at 14 weeks and 0.61±0.13 mm² at 24 weeks.

Mean luminal areas were 1.42±0.15 mm², 1.60±0.17 mm² (P=NS), 1.72±0.13 mm² (P=NS), and 2.13±0.27 mm² (P=.007) at 0, 6, 14, and 24 weeks, respectively (Fig 3, upper left panel). Quantitative coronary angiography performed in coronary arteries of 4 cholesterol-fed pigs with significant plaque growth, as revealed subsequently by histomorphometric analysis, yielded luminal diameters that were not different from those of 3 age-matched control pigs: 2.18±0.025 compared with 2.20±0.085 mm. These values are in agreement with histomorphometric data revealing no decrease in luminal area.

Mean medial areas were 0.89±0.029 mm², 0.93±0.047 mm² (P=NS), 1.34±0.27 mm² (P=NS), and 1.78±0.12 mm² (P<.001) at 0, 6, 14, and 24 weeks, respectively (Fig 3, lower right panel). The number of SMC nuclei in the media was 1990±100 at 6 weeks, 3320±550 at 14 weeks (P=.02), and 3520±390 (P=.0025) at 24 weeks. Medial cell proliferation was demonstrated by focal staining of medial SMCs with PCNA-specific antibodies in atheromatous plaques (Fig 2f) but not in early lesions.

The reactivity of oxidized porcine LDL and of oxidized human LDL in a competition ELISA was very similar. C50 values, ie, concentrations that are required to obtain 50% of antibody binding to immobilized, in vitro oxidized LDL, was 0.025 mg/dL for porcine and 0.020 mg/dL for human oxidized LDL. A 100-fold molar excess of oxidized porcine HDL did not significantly inhibit antibody binding. Previously, we have demonstrated that the C50 values for human MDA-modified and copper-oxidized LDL were identical and that 100-fold higher molar amounts of MDA-modified lysine in serum albumin were required to obtain 50% of antibody binding. The mAb 4E6 was therefore used to quantify levels of oxidized LDL. The reactivity of native and of oxidized LDL was also assessed in an mAb 13F6–based competition ELISA using identical procedures as in the mAb 4E6–based ELISA. C50 values ranged between 0.010 and 0.015 mg/dL for human native LDL, MDA-modified LDL, and copper-oxidized LDL, whereas a 100-fold molar excess of HDL did not significantly inhibit antibody binding. The mAb 13F6 was therefore used to quantify total levels of LDL in coronary atherosclerotic lesions.

mAb 13F6 and mAb 4E6 did not detect immunoreactive material in the coronary arteries of pigs fed normal chow. The levels of total LDL (lower panel), expressed as mean color intensities measured in mAb 13F6–immunostained sections, were 0.031±0.0098, 0.11±0.057 (P=.05), and 0.43±0.082 (P<.001), respectively (Fig 4). The levels of oxidized LDL (upper panel) in the intima, expressed as mean color intensities measured in mAb 4E6–immunostained sections, were 0.034±0.023, 0.11±0.050 (P<.05), and 0.44±0.065 (P<.001), respectively. Because the affinities of mAbs 13F6 and 4E6 for oxidized LDL are very similar, the affinity of mAb 13F6 for native LDL is 1000-fold higher than that of mAb 4E6.
and the fact that the antibodies were used at the same molar concentration, the virtually identical values obtained with both mAbs strongly suggest that LDL in the arterial wall is essentially completely oxidized. The levels of total and of oxidized LDL in the lesions were correlated with the mean intimal areas of those lesions (n = 26, r = 0.82 and r = 0.85, respectively; P < .0001 for both; Fig 5). In contrast, plasma LDL cholesterol levels were not correlated with intimal areas (n = 26, r = 0.26; P = NS).

The levels of oxidized LDL were correlated with both the macrophage-associated intimal areas (r = 0.85, P < .0001) and SMC-associated intimal areas (r = 0.81, P < .0001).

The specificity of immunostaining with mAb 4E6 was confirmed by inhibition of staining with an excess of MDA-modified LDL and of copper-oxidized LDL but not with native LDL or MDA-modified albumin. A concentration-dependent decrease of mean intensities in coronary artery sections of miniature pigs fed the cholesterol diet for 6 weeks was obtained when in vitro oxidized LDL, ranging between 125 (90% inhibition) and 15 (15% inhibition) μg/mL, was added to the antibody solution.

A concentration-dependent decrease of mean intensities in coronary artery sections of miniature pigs fed the cholesterol diet for 24 weeks, with eightfold higher mean intensities than at 6 weeks, was obtained when in vitro oxidized LDL, ranging between 125 (90% inhibition) and 15 (15% inhibition) μg/mL, was added to the antibody solution.

Mean IEL areas were correlated with external elastic lamina areas (r = 0.9, P < .0001; data not shown) and were therefore considered to represent an index of artery size. Mean IEL areas were also correlated with mean intimal areas (r = 0.76, P < .0001), levels of oxidized LDL (r = 0.72, P < .0001), and luminal areas (r = 0.46, P = .019; Fig 6). Mean luminal areas were correlated with mean intimal areas (r = 0.49, P = .010), levels of oxidized LDL (r = 0.50, P = .0098), and mean medial areas (r = 0.46, P = .019; Fig 6).

**Discussion**

The present study demonstrates that cholesterol feeding of miniature pigs results in an increase in plasma levels of total and LDL cholesterol within 6 weeks that is associated with the generation of fatty streaks consisting primarily of macrophages. Although total and LDL cholesterol levels did not increase further between 6 and 24 weeks, fatty streaks in the coronary arteries of LDL-hypercholesterolemic pigs progressed to fibrofatty (14 weeks) and atheromatous (24 weeks) plaques. The latter plaques consisted of a lipid-rich core that contained primarily proliferating monocytes/macrophages and a cap consisting primarily of nonproliferating SMCs. Total and oxidized LDL levels in lesions were strongly correlated (r = 0.90) and almost identical, suggesting that the LDL in plaques is essentially oxidized. The extent of plaque growth was correlated with plaque levels of total and oxidized LDL, which were independent of plasma levels of LDL and of oxidized LDL. These data are in agreement with a model in which LDL hypercholesterolemia is associated with infiltration of LDL into the arterial wall, even when plasma LDL cholesterol levels remain constant, where it becomes oxidized to a large extent. The finding that levels of oxidized LDL in the arterial wall do increase in the absence of an increase in its plasma levels indeed suggests that oxidation of LDL occurs in the arterial wall.

Previously it has been demonstrated that damage or dysfunction of the endothelium may reduce its effectiveness to act as a selectively permeable barrier to plasma components, including cholesterol-rich lipoprotein remnants. Lipid peroxidation can induce endothelial cell injury/dysfunction associated with an increased uptake of LDL in the arterial wall. In the presence of hyperlipoproteinemia, endothelial hyperpermeability and the accumulation of subendothelial matrix proteins may favor intimal uptake and retention of LDL. Accumulation of apoB–100–containing lipoproteins in the arterial wall following hypercholesterolemia induces alterations in the sulfated glycosaminoglycans of matrix proteoglycans, resulting in enhanced retention of these lipoproteins. The reversible interaction of these lipoproteins with altered glycosaminoglycans selects particles with a high affinity that are more prone to oxidation. Fractional rates of efflux of arterial LDL have been found to be decreased in lesion-susceptible areas, suggesting that the focal increases in LDL concentration observed at those
sites are due to localized differences in LDL retention and its rate of degradation.24

Local oxidation of “trapped” LDL may generate lipid-derived inflammatory mediators, such as oxysterols, peroxidized fatty acids, and lysophospholipids, that can induce atherogenic monocyctic inflammatory responses in the arterial wall,25 resulting in the generation of macrophage foam cells and the initiation of fatty streaks.26 LDL hypercholesterolemia in miniature pigs was initially associated with the accumulation of monocytes/macrophages and macrophage foam cells in the subendothelial layer (at 6 weeks) and only later (at 14 and 24 weeks) with the formation of a fibrous cap consisting of SMCs. Oxidized LDL was associated with monocytes/macrophages and macrophage foam cells in the core of the intima but not with SMCs in the fibrous cap, although levels of oxidized LDL were correlated with both the macrophage- and SMC-associated intimal areas. Thus, whereas levels of oxidized LDL may reflect only the number of macrophages in fatty lesions and in the core of the atheromatous plaque, these levels do not only reflect the number of SMCs in the fibrous cap of the atheromatous plaque.

The accumulation of oxidized LDL in the intima was not associated with intimal SMC proliferation, as evidenced by the lack of reactivity with the PCNA-specific antibodies. Fibrous cap formation may therefore result from SMC migration in association with the accumulation in the underlying core of macrophages containing oxidized LDL. Previously it has been demonstrated that oxidized LDL induces SMC migration in vitro,27,28 which is in agreement with the correlation between the plaque levels of oxidized LDL and the extent of fibrous cap formation, in the absence of oxidized LDL accumulation in the SMCs. Moreover, macrophage foam cells generated by the accumulation of oxidized LDL may induce SMC migration.29,30

Previously we have demonstrated that the accumulation of oxidized LDL in coronary atherosclerotic lesions of hypercholesterolemic rabbits was also correlated with plaque growth, which however, was associated with a significant narrowing of the lumen.16 In the present hypercholesterolemic miniature pigs, accumulation of oxidized LDL was associated not only with plaque growth but also with vessel remodeling that compensated for the plaque growth, as suggested by the observed correlations between levels of oxidized LDL and IEL and luminal areas, respectively. Remodeling in arteries of nonhuman primates was found to be very similar to that in human arteries.12 Although the studies in nonhuman primates confirmed a relationship between plasma lipids and intimal areas, these studies did not demonstrate an association between lipids and lumen size variability. The present study confirms the lack of association between plasma lipids and remodeling and more importantly demonstrates an association between levels of oxidized LDL in the plaque and luminal area.

Medial SMC growth was suggested by the focal staining of medial SMCs with PCNA-specific antibodies and the increase in the number of SMCs in the media. In vitro cholesterol loading of macrophages was found to stimulate vascular SMC growth, and macrophage/vascular SMC interactions were found to be reduced by increasing the dietary amounts of fish oil, consistent with favorable modulation of the atherogenic process.34–36 The presence of cholesterol-loaded macrophage foam cells, which may be generated by the uptake of oxidized LDL, in coronary atherosclerotic lesions of hypercholesterolemic pigs but not of hypercholesterolemic rabbits16 may explain why plaque growth in porcine coronary arteries but not in rabbit coronary arteries is associated with medial growth.

The contribution of arterial remodeling to luminal narrowing has been demonstrated after angioplasty in hypercholesterolemic rabbits and micropigs.34–36 The present study demonstrates, for the first time, positive remodeling in response to initial and progressive atherosclerosis that is
associated with LDL hypercholesterolemia in the absence of mechanical overstretch injury and/or endothelial denudation in pigs. Focal compensatory enlargement has been demonstrated in human carotid and coronary arteries in association with atherosclerotic disease,37–39 and lesion progression in one coronary segment was found to be associated with significant increases in the segmental diameter of remote parts of the coronary tree.40 Thus, the present data suggest that this porcine model of coronary atherosclerosis may closely resemble human atherosclerosis and that the miniature pigs used in the present study may be an alternative for primates as animal models to study the mechanisms underlying human coronary atherosclerosis. This model may also be useful for evaluating the effect of antioxidant therapy on the generation of oxidized LDL in the arterial wall and the progression of atherosclerosis.

In conclusion, although the present data did not allow us to demonstrate a causal role for oxidized LDL, they are in agreement with a model in which LDL hypercholesterolemia is associated with LDL infiltration at constant plasma levels of LDL and of oxidized LDL and with oxidation of LDL in the arterial wall. Plaque levels of oxidized LDL can be correlated with both plaque burden and appropriate remodeling in coronary arteries of hypercholesterolemic miniature pigs.

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