Role of Lipoproteins and Inflammation in the Progression/Regression of Atherosclerosis

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Pathophysiology of Atherosclerosis: the Mechanisms of Progression

1. Lipoproteins
2. Inflammation and progression of atherosclerosis
3. Lipoproteins and inflammation
Progression (MLD decrease), mm/yr

Angiographic Progression Rate by LDL-C Achieved in Statin Trials

QCA of the mid LAD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD</td>
<td>1.39 mm</td>
</tr>
<tr>
<td>% diameter stenosis</td>
<td>30 %</td>
</tr>
<tr>
<td>Reference diameter</td>
<td>1.99 mm</td>
</tr>
<tr>
<td>Position reference diameter</td>
<td>13.38 mm</td>
</tr>
<tr>
<td>Length stenotic segment</td>
<td>53.01 mm</td>
</tr>
<tr>
<td>Position of proximal border</td>
<td>4.53 mm</td>
</tr>
<tr>
<td>Position of distal border</td>
<td>57.72 mm</td>
</tr>
<tr>
<td>Minimum area absolute</td>
<td>0.33 mm²</td>
</tr>
<tr>
<td>MLA densitometry</td>
<td>1.97 mm²</td>
</tr>
<tr>
<td>MLA circular</td>
<td>1.52 mm²</td>
</tr>
<tr>
<td>% area stenosis densitometry</td>
<td>37 %</td>
</tr>
<tr>
<td>% area stenosis circular</td>
<td>51 %</td>
</tr>
<tr>
<td>Reference area</td>
<td>3.10 mm²</td>
</tr>
</tbody>
</table>

Diagram showing measurements and analysis.
Outcome variable: change in percent diameter stenosis for all stenoses > 25% at baseline

\[
\text{Percent diameter stenosis} = \frac{\text{Reference Diameter} - \text{Minimum Lumen Diameter}}{\text{Reference Diameter}} \times 100
\]
ASTEROID: Angiographic Regression

292 patients with at least 1 segment containing >25% stenosis

Mean Δ Percent Diameter Stenosis

Δ -1.3%

Baseline

Follow-up

Median Δ %DS: -0.50% (-4.00, 2.00)
p < 0.001

LDL-C: 131.5 mg/dL

LDL-C: 61.1 mg/dL

Mean Δ Minimum Lumen Diameter

Δ +0.03 mm

Baseline

Follow-up

Median Δ MLD: +0.02 (-0.04, 0.11) mm
p < 0.001

Change in % Diameter Stenosis vs On-Treatment LDL-C in QCA Trials

Change in % Stenosis per year

On-Treatment LDL-C (mg/dL)

Placebo
Statin*

R² = 0.78
p = 0.0003

* ASTEROID rosuvastatin
CCAIT lovastatin
LCAS fluvastatin
MAAS simvastatin
MARS lovastatin
PLAC I pravastatin

Change in Percent Diameter Stenosis vs On-treatment HDL-C in QCA Trials

*ASTEROID rosuvastatin  MAAS simvastatin  CCAIT lovastatin
MARS lovastatin  LCAS fluvastatin  PLAC I pravastatin

Angiographic Effects of Lipid Drug Classes Meta-Analysis, 12 Trials

\[ \Delta \% s = 3.0 - 0.076 (\% \Delta \text{HDL-C}) + 0.06 (\% \Delta \text{LDL-C}) \]

\[ R^2 = 0.96; P < .004 \]


S+N=simvastatin + niacin

* HATS (HDL-atherosclerosis treatment study) data not shown in original study
Angiographic Effects of Lipid Drug Classes
Meta-Analysis, 12 Trials

Change from Baseline in Mean Proximal % Stenosis

$\Delta\%s = 3.0 - 0.076 (\%\Delta\text{HDL-C}) + 0.06 (\%\Delta\text{LDL-C})$
$R^2 = 0.96; P<.004$

Progression
Regression

HATS* Placebo
Placebo (6)
Fibrates (1)
Statins (6)
Statin+Resin (1)
Niacin Combos (4)

HATS* S+N

S+N=simvastatin + niacin
* HATS (HDL-atherosclerosis treatment study) data not shown in original study
Angiography Does Not Image Plaque
Discord between Lumen and Atherosclerosis
Recent Coronary IVUS Progression Trials: Relation between LDL-C and Progression Rate

Median change in percent atheroma volume (%) vs Mean LDL-C (mg/dL)

- ASTEROID rosvastatin
- REVERSAL atorvastatin
- REVERSAL placebo
- ACTIVATE placebo
- CAMELOT pravastatin

$\text{r}^2 = 0.95$

$p < 0.001$

Beneficial Impact of Lowering LDL-C:HDL-C Ratio on Atherosclerosis

Nicholls S et al. *JAMA* 2007;297:499–508
What is the significance of progression as measured by QCA (i.e., luminal narrowing)?

- Patients with the most progression have the highest rate of CAD
- Progression of CAD as measured by QCA has been shown to predict clinical CV events such as MI, CAD mortality, and need for revascularization in the following studies:
  - Program for the Surgical Control of the Hyperlipidemias
  - Montreal Heart Institute study of nicardipine
  - Cholesterol Lowering Atherosclerosis Study
Changes in lumen dimension over time correlated weakly with IVUS parameters

- Relationship between QCA and IVUS at single time points (n=525) and changes over time (n=432)
- Statistically significant correlations were observed between QCA coronary artery score and IVUS-derived lumen volume (r=0.65, P<0.0001) and total vessel volume (r=0.55, P<0.0001)
- Statistically significant but weak correlations between changes over time in lumen dimensions on QCA and IVUS (r=0.14, P<0.01)
- Nevertheless, pts with and without angiographic progression had changes in plaque volume on IVUS of 9.13 and 0.20 mm³ (P=0.08)

IVUS vs. QCA

**IVUS**
- Measures wall precisely (not atheroma)
- Measures disease in a single proximal artery without critical disease, ie focuses on the portion with the LEAST luminal narrowing
- More precise method to measure changes in vessel wall and lumen size for CAD
- Clinical significance of progression and regression?

**QCA**
- Measures lumen dimension
- Examines the entire coronary bed including branches
- Focuses on the portion with the GREATEST luminal narrowing
- More sensitive to picking of thrombotic luminal narrowing due to atherothrombotic events anywhere in coronary bed
- Progression as defined by QCA predicts clinical events
- Significance of regression in regards to clinical events unclear
MCVE Frequency by LDL and HDL levels in TNT

Barter et al, NEJM 2007, 357; 13, 1301-1310
SATURN

1300 patients with symptomatic CAD (angiographic stenosis >20%)
LDL-C with (>80 mg/dL) or without (>100 mg/dL) statin use last 4 weeks

Visit: 1  2  3  4  5  6  7  8  9  10  11
Week:  -4  -2  0  13  26  39  52  65  78  91  104

* Safety assessments

Screening Period

Randomization Period
ORION: Example of Change in Plaque Composition over 2 Years with Rosuvastatin Treatment

T1W=T1-weighted; TOF=time-of-flight; PD=proton density; T2W=T2-weighted; *=lumen; JV=jugular vein

Underhill HR et al. Am Heart J 2008; 155: 584.e1–e8
ORION: Reduction in LDL-C and Lipid-Rich Necrotic Core with Rosuvastatin

Mean change from baseline (%)

Rosuvastatin 5 mg  Rosuvastatin 40 mg

LDL-C

% LRNC

N=8

N=10

*P <0.001 vs baseline
†P =0.014 vs baseline
‡P <0.001 rosuvastatin 40 mg vs rosuvastatin 5 mg

Endothelial Dysfunction in Atherosclerosis

Fatty-Streak Formation in Atherosclerosis

Formation of an Advanced, Complicated Lesion in Atherosclerosis

Unstable Fibrous Plaques in Atherosclerosis

Lipoprotein Classes and Inflammation

Chylomicrons, VLDL, and their catabolic remnants

> 30 nm
Potentially proinflammatory

LDL

20–22 nm

HDL

9–15 nm
Potentially anti-inflammatory

Role of LDL in Inflammation

LDL Readily Enter the Artery Wall Where They May be Modified

Vessel Lumen

LDL

Oxidation of Lipids and ApoB

Hydrolysis of Phosphatidylcholine to Lysophosphatidylcholine

Aggregation

Other Chemical Modifications

Modified LDL

Modified LDL are Proinflammatory

Endothelium

Intima

Adhesion molecules mediate leukocyte migration

Characteristics of Monocytes from Blood of ApoE−/− Mice on High-Fat Diet

Blood CD11c+ cells

WT

apoE−/−

Neat Stain

Oil Red O staining

Electron microscopy

The majority of foamy monocytes were CD11c+ in blood of apoE<sup>−/−</sup> mice on HFD.

CD11c and VLA-4 cooperate in monocyte capture and firm arrest

MNCs arrested at 2 dyne/cm²

60% decrease  75% decrease

CD11c and VLA-4 contributions are not additive. They cooperate to mediate efficient monocyte arrest on VCAM-1

CD11c and Atherosclerosis in ApoE−/− Mice

Sudan IV staining of mouse aortas

Deficiency of CD11c decreases macrophage contents in atherosclerotic lesions of apoE−/− mice

A Model for Involvement of CD11c in Atherogenesis in Hypercholesterolemia

CD11c/CD18 Expression Is Upregulated on Blood Monocytes During Hypertriglyceridemia and Enhances Adhesion to Vascular Cell Adhesion Molecule-1


Objective—Atherosclerosis is associated with monocyte adhesion to the arterial wall that involves integrin activation and emigration across inflamed endothelium. Involvement of β2-integrin CD11c/CD18 in atherogenesis was recently shown in dyslipidemic mice, which motivates our study of its inflammatory function during hypertriglyceridemia in humans.

Methods and Results—Flow cytometry of blood from healthy subjects fed a standardized high-fat meal revealed that at 3.5 hours postprandial, monocyte CD11c surface expression was elevated, and the extent of upregulation correlated with blood triglycerides. Monocytes from postprandial blood exhibited an increased light scatter profile, which correlated with elevated CD11c expression and uptake of lipid particles. Purified monocytes internalized triglyceride-rich lipoproteins isolated from postprandial blood through low-density lipoprotein–receptor–related protein–1, and this also elicited CD11c upregulation. Laboratory-on-a-chip analysis of whole blood showed that monocyte arrest on a vascular cell adhesion molecule–1 (VCAM-1) substrate under shear flow was elevated at 3.5 hours and correlated with blood triglyceride and CD11c expression. At 7 hours postprandial, blood triglycerides decreased and monocyte CD11c expression and arrest on VCAM-1 returned to fasting levels.

Conclusion—During hypertriglyceridemia, monocytes internalize lipids, upregulate CD11c, and increase adhesion to VCAM-1. These data suggest that analysis of monocyte inflammation may provide an additional framework for evaluating individual susceptibility to cardiovascular disease. (Arterioscler Thromb Vasc Biol. 2011;31:00-00.)
Inflammation in Adipose Tissue is Present with Obesity and Plays a Crucial Role in Obesity Related Insulin Resistance

- Increased expression of inflammatory genes in white adipose tissue of mice with obesity due to genetic causes, greatest increase in obesity induced by very high fat diet
- Macrophages present in adipose tissue and reduced by treatment with rosiglitazone
- Positive correlation between macrophage markers, BMI, and adipocyte size in both mouse and man
- Bone marrow transplants and macrophage deficient mice show most are CSF-1 dependent, bone marrow derived
- Most TNF alpha in adipose tissue derived from macrophages

Obese Adipose Tissue is Characterized by Inflammation and Progressive Infiltration by Macrophages as Obesity Develops

Potential Mechanisms for Activation of Inflammation in Adipose Tissue

Overflow Hypothesis

1. Lean
2. Intervention (fat feeding)
3. Primary Hepatic Resistance
4. Hepatic + Peripheral Resistance

Visceral Depot
Peripheral Depot
Local, Portal, and Systemic Effects of Inflammation in Insulin Resistance and Atherogenesis

**CD11c, CD11b, and MCP-1 in Human AT or Blood**

**Relationship of MCP-1 with CD11c in human VAT**

- \( r = 0.82 \)
- \( P < 0.01 \)

**Monocyte CD11c level on human monocytes**

- Lean
- Obese
- Obese-WL

- \( P < 0.01 \)
- \( P < 0.05 \)

**Relationship of MCP-1 with CD11b in human VAT**

- \( r = 0.66 \)
- \( P < 0.01 \)

**Relationship of monocyte CD11c with HOMA-IR in humans**

- \( r = 0.57 \)
- \( P < 0.01 \)

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Can Anti-Inflammatory Therapy Reduce Cardiometabolic Risk?

• High-dose sodium salicylate shown to reduce glycosuria\textsuperscript{1,2}
• Small studies showed reduction in fasting glucose with high-dose ASA\textsuperscript{3,4}
• Effects of ASA on I\text{KK}/NF-\text{\kappa}B axis\textsuperscript{5,6}
• May explain some benefits seen with TZD and ACE on diabetes prevention

1. Ebstein W. *Berliner Klinische Wochenschrift* 1876;13:337
2. Williamson RT. *BMJ* 1901;1:760
3. Reid et al. *BMJ* 1957;2:1071
4. Hecht A et al. *Metabolism* 1959;8:418
Can Anti-Inflammatory Therapy Reduce Cardiometabolic Risk?

- MCP-1 and CCR2 are increased in adipose tissue with obesity.
- CCR2 deficient mice had modest reduction in adipose inflammation, increased adiponectin, reduced hepatic steatosis and improved systemic glucose homeostasis.
- Short term rx with CCR2 antagonist in mice with diet induced obesity did not alter weight, modest reduction in macrophages in adipose tissue with improved HOMA-IR.

The Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial (STABILITY)

- 15,828 men and women with CHD and ≥1 of the following:
  - age ≥60 years
  - Diabetes requiring medication
  - Low HDL-C
  - Current or recent smoking
  - Mildly or moderately reduced kidney function
  - Cerebrovascular disease or PAD

- Randomized to darapladib 160 mg/d or placebo; each in addition to standard therapy

- **Primary endpoint**: Time to the first MACE: CV death, nonfatal myocardial infarction, nonfatal stroke

- Anticipated study duration: 2.75 years (median)

Summary

1. LDL and HDL are associated with progression of atherosclerosis and atherothrombotic events
2. LDL contributes to vascular inflammation; HDL may inhibit this process
3. Chronic inflammation promotes vascular inflammation and may increase atherogenicity of lipoproteins
4. Obesity, metabolic syndrome, and diabetes are associated with chronic inflammation, leukocyte activation, and dyslipidemia