Postprandial Hyperlipidemia and Atherosclerosis

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COI Disclosure

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① Consultation fees: Kowa, Sanwakagaku Kenkyusho, Skylight Biotec
② Stock ownership/profit: none
③ Patent fees: none
④ Remuneration for lecture: MSD, Bayer, Kowa
⑤ Manuscript fees: none
⑥ Trust research/joint research funds: Kowa, Sanwakagaku Kenkyusho, Otsuka, Shionogi, Boehringer Ingelheim, Japan Boehringer Ingelheim, MSD, Bayer, Astellas, Kissei, Fujirebio
⑦ Scholarship fund: none
⑧ Affiliation with endowed department: none
⑨ Other remuneration such as gifts: none
Topics

- Residual Coronary Risks
- Clinical Significance of Hypertriglyceridemia and Increased Remnants
- Methods for Evaluation of Remnants
- Apo B-48 Levels in Relation to Diseases
- Postprandial Hyperlipidemia and Atherosclerosis
- Treatment of Postprandial Hyperlipidemia
Residual Coronary Risks


<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (%)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>30%</td>
<td>10-40mg</td>
</tr>
<tr>
<td>HIPS</td>
<td>13%</td>
<td>40mg</td>
</tr>
<tr>
<td>CARE</td>
<td>24%</td>
<td>40mg</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>31%</td>
<td>40mg</td>
</tr>
<tr>
<td>LIPLD</td>
<td>24%</td>
<td>40mg</td>
</tr>
<tr>
<td>PROSPER</td>
<td>15%</td>
<td>40mg</td>
</tr>
<tr>
<td>CARDS</td>
<td>37%</td>
<td>10mg</td>
</tr>
<tr>
<td>ASCOT</td>
<td>36%</td>
<td>10mg</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>37%</td>
<td>20-40mg</td>
</tr>
<tr>
<td>JUPITER</td>
<td>44%</td>
<td>20mg</td>
</tr>
</tbody>
</table>

*Relative Risk / Relative Hazard (%)

Simvastatin 40mg 70%
Pravastatin 40mg 76%
Atorvastatin 10mg 63%
Rosuvastatin 10mg 64%
Pravastatin 20mg 63%

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Statin can reduce the CV risk by 20-35%, but there are still residual event risks after cholesterol-lowering therapy. Furthermore, coronary plaques regress very limitedly on IVUS and we cannot usually see the widening of vessel lumen.

The reduction of LDL-C alone may not be adequate?

Beyond LDL-cholesterol
Beyond LDL-cholesterol (Residual risk)

- Hypertension
- Diabetes mellitus
- Metabolic syndrome
- Low HDL-C
- Hypertriglyceridemia and postprandial hyperlipidemia
- Inflammation
- Smoking
Triglycerides and Coronary Heart Disease
(11,068 Japanese Cases Followed for 15.5 Years)

(Matched for Age, BMI, TC, Smoking, BP, Alcohol, Blood sugar, Time after Meal, and Menopause)

<table>
<thead>
<tr>
<th>Serum TG (mg/dL)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;84</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>84~116</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>116~166</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>≥166</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

Relative risk

* : p<0.05  *** : p<0.001


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Plasma TG Level Is A Risk Factor For Cardiovascular Disease Independent of HDL-C Level: A Meta-analysis of 17 Population-based Prospective Studies

Exogenous and Endogenous Pathways of Lipoproteins

LDL Receptor

Remnant Receptor

B48

B100

B100

B100

HDL

LDL

VLDL

IDL

Peripheral Tissues

Free Cholesterol

Liver

Chylomicron

Chylomicron Remnant

Intestine

Dietary Cholesterol

Bile Acids + Cholesterol

Intestine

B48

B48

Fatty Acid Lipase

FFA

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Atherogenicity of Lipoprotein Abnormalities Associated with Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Lipoproteins</th>
<th>Atherogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons $\uparrow$</td>
<td>$(-)$</td>
</tr>
<tr>
<td>VLDL $\uparrow$</td>
<td>$(\pm)$ ~</td>
</tr>
<tr>
<td>CM &amp; VLDL remnants $\uparrow$</td>
<td>$(++)$</td>
</tr>
<tr>
<td>Small dense LDL $\uparrow$</td>
<td>$(++)$</td>
</tr>
<tr>
<td>HDL-C $\downarrow$</td>
<td>$(++)$</td>
</tr>
</tbody>
</table>
What Are Remnants?

Chylomicron $\xrightarrow{\text{LPL}}$ Chylomicron Remnant

VLDL $\xrightarrow{\text{LPL}}$ IDL (VLDL Remnant) $\xrightarrow{\text{HTGL}}$ LDL
<table>
<thead>
<tr>
<th></th>
<th>Myocardial Infarction</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>70</td>
<td>23</td>
</tr>
<tr>
<td>T-CH</td>
<td>208 ± 44</td>
<td>197 ± 31</td>
</tr>
<tr>
<td>TG</td>
<td>158 ± 84*</td>
<td>116 ± 63</td>
</tr>
<tr>
<td>HDL-C</td>
<td>36 ± 8***</td>
<td>48 ± 14</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>24 ± 18</td>
<td>16 ± 15</td>
</tr>
<tr>
<td>VLDL-TG</td>
<td>83 ± 73</td>
<td>59 ± 52</td>
</tr>
<tr>
<td>VLDL-(C/TG)</td>
<td>0.31 ± 0.07*</td>
<td>0.27 ± 0.08</td>
</tr>
<tr>
<td>IDL-C</td>
<td>11 ± 5*</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>IDL-TG</td>
<td>15 ± 10*</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>LDL-C</td>
<td>136 ± 41</td>
<td>124 ± 27</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>T-CH</td>
<td>237 ± 47</td>
<td>209 ± 45</td>
</tr>
<tr>
<td>TG</td>
<td>161 ± 57***</td>
<td>82 ± 21</td>
</tr>
<tr>
<td>HDL-C</td>
<td>41 ± 11**</td>
<td>57 ± 19</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>24 ± 23*</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>VLDL-TG</td>
<td>77 ± 84</td>
<td>30 ± 15</td>
</tr>
<tr>
<td>VLDL-(C/TG)</td>
<td>0.31 ± 0.07</td>
<td>0.26 ± 0.10</td>
</tr>
<tr>
<td>IDL-C</td>
<td>17 ± 9*</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>IDL-TG</td>
<td>20 ± 8***</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>LDL-C</td>
<td>156 ± 36</td>
<td>135 ± 27</td>
</tr>
</tbody>
</table>

* Indicates statistically significant difference from control group.
** Indicates highly statistically significant difference from control group.
*** Indicates extremely highly statistically significant difference from control group.
Determination of Remnants

- **Electrophoresis**
  - Agarose electrophoresis (broad β pattern)
  - PAG electrophoresis (midband, broad β pattern)

- **Ultracentrifugation**
  - IDL-cholesterol

- **Immunoaffinity chromatography**
  - RLP-cholesterol, RLP-TG

- **Direct method**（RemL-C）

- **Apo B-48**（ELISA, CLEIA）
PAG Disc Electrophoresis

- **Midband**
  - VLDL
  - LDL
  - HDL

**Parameters**

- TC 231 mg/dl
- TG 367 mg/dl
- HDL-C 35 mg/dl

**Remnants**

- Small dense LDL
- TC 192 mg/dl
- TG 85 mg/dl
- HDL-C 56 mg/dl
Methods for Measuring RLP-C (JIMRO)

**FDA Approved:**
- Risk for CHD (2000)
- Diagnosis of Familial Type III Hyperlipidemia (1999)

**Procedure:**
1. Incubation with Anti Apo A-1, B-100 Antibodies Attached with Sepharose Beads for 3 Hours
2. Low-speed centrifugation
3. Remnant-like Particles (RLP): Unadsorbed Fraction
4. Adsorbed lipoproteins Precipitated

Fig. 1 Schematic procedure of separation and determination of remnant-like particles.
Remnants Are the Critical Risk Factor of Cardiovascular Events


Subjects: patients with cardiovascular events 147 cases male 97 cases, age 65 ± 9.7 years
Study duration: 26.8 ± 13.9 months

\[ p = 0.003 \]
(log-rank test)
Why Are Remnants Important?

- Chylomicron remnants and VLDL remnants (IDL) are taken up by macrophages without oxidation, forming foam cells.

- It is important to assess the increase of remnants and decrease them, which leads to the attenuation of development of atherosclerotic cardiovascular diseases.
Chylomicron Remnants Contribute to Form Atherosclerotic Lesions Via Several Mechanisms

Chylomicron Remnants

Influx and retention in vascular wall

Small dense LDL↑
HDL-C↓

Inflammation↑
Egr-1, MCP-1, IL-1β, CD40, and others

Endothelial cells
PAI-1↑
apoptosis↑
endothelial dysfunction↑

Macrophages
Foam cell formation↑

Smooth muscle cells
Proliferation↑

Atherosclerotic lesion formation

Measurement of fasting serum apoB-48 levels in normolipidemic and hyperlipidemic subjects by ELISA

Naohiko Sakai, Yoshiaki Uchida, Koji Ohashi, Toshiyuki Hibuse, Yasuhiko Saika, Yoshiaki Tomari, Shinji Kihara, Hisatoyo Hiraoka, Tadashi Nakamura, Satoru Ito, Shizuya Yamashita, and Yuji Matsuzawa

Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine, B5, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; and Diagnostic Research Laboratories, Fujirebio, Inc., 51 Komiya-cho, Hachioji, Tokyo 192-0031, Japan

Schematic Representation of apoB-48 Assay Procedure by 2-Step Sandwich ELISA


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Distribution of Fasting Serum Apo B48 Levels in CAD and Non-CAD Subjects

### Fasting ApoB-48 Level Is Correlated with Prevalence of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate p value</th>
<th>Multivariate p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>0.1581</td>
<td>-</td>
</tr>
<tr>
<td>sex</td>
<td>0.3698</td>
<td>-</td>
</tr>
<tr>
<td>Log-BMI</td>
<td>0.4645</td>
<td>-</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.0492</td>
<td>-</td>
</tr>
<tr>
<td>TC</td>
<td>0.7440</td>
<td>-</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.8508</td>
<td>-</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.0085</td>
<td>0.3721</td>
</tr>
<tr>
<td>TG</td>
<td>0.0017</td>
<td>0.1098</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.9747</td>
<td>-</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.6757</td>
<td>-</td>
</tr>
<tr>
<td>FPG</td>
<td>0.0081</td>
<td>0.6110</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.0008</td>
<td>0.3036</td>
</tr>
<tr>
<td>Log-apoB-48</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log-APN</td>
<td>0.0239</td>
<td>0.6039</td>
</tr>
</tbody>
</table>

Univariate and Multivariate Analyses of correlations between CHD and various parameters
Univariate: Pearson's correlation analysis, Multivariate: Stepwise multiple regression analysis.

Postprandial Hyperlipidemia

- Increased TG-rich chylomicron remnants after meals
- Hypertriglycerideridemia is prolonged after meals
- Highly atherogenic state

Zilversmit DB: Circulation 60:473-85, 1979
Postprandial Hyperlipidemia in Patients with Type IIb Hyperlipidemia

- TG peak is prolonged
- TG reduction is impaired
- High TG level at fasting

- TG peak is 3-4 h after meal in control subjects
- Returns to fasting TG level after 6-8 h
Postprandial Hyperlipidemia in Patients with Coronary Heart Disease

fatty meal contained 729 kcal per square meter of body surface and consisted of 5.3 g protein, 24.75 g carbohydrate, 240 mg cholesterol, and 65.2 g fat (from heavy whipping cream) with a polyunsaturated to saturated fat ratio of 0.06

Patsh JR et al: ATVB 12:1336-1345, 1992
Postprandial Hyperlipidemia Is a Risk for Coronary Artery Disease Mortality

Accumulated Mortality (% Due to Coronary Artery Disease)

Subjects Enrolled in MRFIT Study (n=2,809)

- Non-fasting TG ≥ 200mg/dL (Mean 376.0±197.2mg/dL)
- Non-fasting TG < 200mg/dL (Mean 138.7±37.5mg/dL)

Postprandial Hyperlipidemia (Non-fasting Hypertriglyceridemia) Is a Critical Risk Factor of Cardiovascular Events in a Japanese Population

Subjects: Normocholesterolemic Japanese (n=1,068)


* p<0.05, ** p<0.01, *** p<0.001
### Odds Ratio for Ischemic Stroke in Relation to Non-fasting TG and Total Cholesterol Levels

**Copenhagen City Heart Study**

<table>
<thead>
<tr>
<th>TG (mg/dL)</th>
<th>Age-adjusted</th>
<th>Multivariate adjusted *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>&lt;89</td>
<td>2,210 (29) / 183</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>89~176</td>
<td>3,985 (53) / 451</td>
<td>p=0.17</td>
</tr>
<tr>
<td>177~265</td>
<td>985 (13) / 146</td>
<td>8</td>
</tr>
<tr>
<td>266~353</td>
<td>241 (3) / 29</td>
<td>15</td>
</tr>
<tr>
<td>354~442</td>
<td>96 (1) / 17</td>
<td>11</td>
</tr>
<tr>
<td>≥443</td>
<td>62 (1) / 11</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Chol (mg/dL)</th>
<th>Patients number(%) / Events</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;193</td>
<td>1,167 (15) / 76</td>
<td></td>
</tr>
<tr>
<td>193~231</td>
<td>2,246 (30) / 218</td>
<td></td>
</tr>
<tr>
<td>232~270</td>
<td>2,197 (29) / 259</td>
<td></td>
</tr>
<tr>
<td>271~308</td>
<td>1,300 (17) / 187</td>
<td></td>
</tr>
<tr>
<td>309~347</td>
<td>480 (6) / 69</td>
<td></td>
</tr>
<tr>
<td>≥348</td>
<td>189 (2) / 28</td>
<td></td>
</tr>
</tbody>
</table>

Factors and Diseases Affecting Postprandial Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Extent of change in postprandial lipaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary factors</td>
</tr>
<tr>
<td>Amount of fat (meal)</td>
</tr>
<tr>
<td>Type of fat (meal)</td>
</tr>
<tr>
<td>Type of fat (habitual diet)</td>
</tr>
<tr>
<td>Carbohydrates</td>
</tr>
<tr>
<td>Protein (meal)</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Fibre</td>
</tr>
<tr>
<td>Lifestyle factors</td>
</tr>
<tr>
<td>Physical exercise</td>
</tr>
<tr>
<td>Tobacco use</td>
</tr>
<tr>
<td>Physiological factors</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Menopausal status</td>
</tr>
<tr>
<td>Physiopathology</td>
</tr>
<tr>
<td>Fasting triacylglycerolaemia</td>
</tr>
<tr>
<td>Central obesity</td>
</tr>
<tr>
<td>Insulin resistance/type</td>
</tr>
<tr>
<td>2 diabetes</td>
</tr>
</tbody>
</table>

Drug Treatment of Postprandial Hyperlipidemia

- Statins
- Fibrates
- Inhibitors of intestinal cholesterol transporter (ezetimibe)
- EPA, ω-3 fatty acids (EPA/DHA)
- Anti-diabetic drugs
- Others
Effect of Pitavastatin on Chylomicron Secretion into Lymph after OFL of Rats

Administration of Fenofibrate Reduces Fasting and Postprandial Plasma Triglyceride Concentrations in Wild-type and CD36-null Mice

![Graph showing the effect of fenofibrate on triglyceride levels in wild-type (WT) and CD36-null (CD36 KO) mice.](image)

- Fasting
  - Chow diet
  - Chow diet + Fenofibrate 0.05%
  - *p<0.05

- Postprandial
  - WT n=20
  - CD36 KO n=20

*Chow diet* vs. *Chow diet + Fenofibrate 0.05%*
Target of Ezetimibe

Dietary cholesterol (250-500 mg) → Cholesterol Intake

Biliary cholesterol (1,000 mg) → Cholesterol Intake

Luminal Cholesterol → Bile Acids → Micellar Cholesterol → Absorption ~50%

Ezetimibe → ABCG5, ABCG8, SR-B1, NPC1L1

Cholesterol Esters → Phytosterols → ACAT2, CM, ABCAI, LDL-R

Ezetimibe inhibits NPC1L1, reducing the absorption of dietary cholesterol.
Subjects

Patients with Type IIb Hyperlipidemia (n=10, 8 Males and 2 Females)
Age: 51 ± 14 years (34-67)
BMI: 27.1 ± 4.4 kg/m²

1. Total cholesterol ≥ 220 mg/dl and TG ≥ 150 mg/dl at fasting
2. Patients were administered ezetimibe (10mg/day) with informed consent
3. This study was approved by Ethical Committee of Osaka University Hospital
Effects of Ezetimibe on Postprandial Hyperlipidemia

Ezetimibe Reduces Postprandial Cholesterol and TG Levels in WT and CD36KO Mice

**Graphs:**

- **TG (mg/dl):**
  - WT chow diet:
    - Fasting: Diet alone vs. Diet + Ezetimibe
    - Postprandial: Diet alone vs. Diet + Ezetimibe
  - WT western diet:
    - Fasting: Diet alone vs. Diet + Ezetimibe
    - Postprandial: Diet alone vs. Diet + Ezetimibe
  - CD36KO chow diet:
    - Fasting: Diet alone vs. Diet + Ezetimibe
    - Postprandial: Diet alone vs. Diet + Ezetimibe

- **TC (mg/dl):**
  - WT western diet:
    - Fasting: Diet alone vs. Diet + Ezetimibe
    - Postprandial: Diet alone vs. Diet + Ezetimibe
  - CD36KO chow diet:
    - Fasting: Diet alone vs. Diet + Ezetimibe
    - Postprandial: Diet alone vs. Diet + Ezetimibe

**Statistical Significance:**

- Symbols: * indicate statistical significance.
Ezetimibe Reduces Intestinal Absorption of $^3$H-labeled Trioleate in Both CD36KO and WT Mice

Intestinal absorption of labeled trioleate is decreased by ezetimibe in CD36KO mice

Intestinal absorption of labeled triolein is decreased by ezetimibe in WT mice fed a western diet

$*$ p<0.05
Fatty Acids
DG, TG

ABCG5/8

Absorption of FFAs
FABP1
FATP4
FABP2

DDAT1
DDAT2
MGAT2

ACAT2

Cholesteryl esters

PL
TG

Ezetimibe

Ezetimibe

ApoB mRNA

ApoB48

LDL-R

LDL

CM Remnants

Plasma

CM

Lymph

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Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)  
p=0.016

Simva — 34.7%  
2742 events

EZ/Simva — 32.7%  
2572 events

NNT = 50

7-year event rates
**IMPROVE-IT**

**Primary and 3 Prespecified Secondary Endpoints — ITT**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Event Rate (%)</th>
<th>Simva*</th>
<th>EZ/Simva*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary CVD/MI/UA/Cor Revasc/CVA</td>
<td>0.936</td>
<td>34.7</td>
<td>32.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Secondary #1 All D/MI/UA/Cor Revasc/CVA</td>
<td>0.948</td>
<td>40.3</td>
<td>38.7</td>
<td>0.034</td>
</tr>
<tr>
<td>Secondary #2 CHD/MI/Urgent Cor Revasc</td>
<td>0.912</td>
<td>18.9</td>
<td>17.5</td>
<td>0.016</td>
</tr>
<tr>
<td>Secondary #3 CVD/MI/UA/All Revasc/CVA</td>
<td>0.945</td>
<td>36.2</td>
<td>34.5</td>
<td>0.035</td>
</tr>
</tbody>
</table>

*7-year event rates (%)

**UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)**
Take home messages

- Postprandial hyperlipidemia is a strong risk factor for CHD due to increases in chylomicron remnants.
- Postprandial hyperlipidemia is often observed in patients with diabetes, metabolic syndrome and CHD.
- Postprandial hyperlipidemia can be treated with diet/exercise and anti-hyperlipidemic drugs such as statins, fibrates and intestinal cholesterol transporter inhibitor (ezetimibe).
- Inhibition of cholesterol absorption by ezetimibe on top of statin even at very low LDL-C levels prevented CV events in patients with ACS.