Lipoprotein Transport in the Metabolic Syndrome: Integrative Lessons from Tracer Studies

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Dyslipidaemia and Obesity is Central to Metabolic Syndrome
Stable Isotope Tracer Studies

Fasting bloods collection, 10 hours 24, 48, 72 and 96 hours

D₃-leucine injection

**Barrett, Chan, Watts J Lipid Res 2006;**

**Kinetic parameters:**
- **Production rate**
  Rate at which protein moves through a pool
- **Fractional catabolic rate**
  Fraction of the protein lost irreversibly from a pool per unit time

Gas chromatography-mass spectrometry

Generate tracer data

VLDL HDL

Apo A

Apo B
Metabolic Syndrome: Dysregulation of ApoB and ApoA-I Containing Lipoproteins

Dyslipidaemia

The relationship between VLDL$_1$ secretion and Liver Fat assessed by NMR spectroscopy

Liver fat content is the driving force behind oversecretion of large VLDL particles

Watts et al. Obesity Research 2003; 11: 152/
Chan et al. ATVB; 2004: 2188-91
Alterations in energy balance lead to excess liver fat and oversecretion of VLDL-TG

- Increased rate of fat import results in increased rate of hepatic FFA uptake and TG synthesis and availability

- Insulin resistance and excess dietary sugars upregulates SREBP-1c, ChREBP and Fox01 pathways, enhancing hepatic de novo lipogenesis, fat accumulation and VLDL production

If fat oxidation and secretion of VLDL particles is NOT able to adequately compensate for excess hepatic TG availability, fat accumulates in hepatocytes, reflecting the imbalance between import and export of lipids from the liver.
ApoC-III is a determinant of VLDL$_1$ TG FCR

Taskinen M-R et al. ATVB 31(9):2144-2150, 2011
Determinants of VLDL₁ TG secretion and catabolic rates in abdominal obese subjects


\[ r = 0.64 \quad P < 0.0001 \]

\[ r = -0.53 \quad P < 0.001 \]
Expansion in VLDL Pool and related features of Insulin Resistance are Central to the Pathogenesis of Dyslipoproteinaemia in the Metabolic Syndrome

Annette T. Y. Wong, Dick C. Chan, Jing Pang, Gerald F. Watts, and P. Hugh R. Barrett

Conclusion: We demonstrate that postprandial hypertriglyceridemia in central obesity relates to an overproduction and impaired catabolism of apoB-48-containing lipoproteins. These findings are based on a new, physiologically relevant, kinetic model, which describes the non-steady-state postprandial metabolism of apoB-48. (J Clin Endocrinol Metab 99: E122–E126, 2014)
Therapeutic Interventions

- **Lifestyle**
  - Weight loss
  - Diet
  - Exercise

- **Pharmacotherapy**
  - Statins
  - n-3 PUFAs
  - PPARs (α, δ, γ)
  - Ezetimibe
  - Niacin
  - CETP inhibitors
ApoB and ApoAI Kinetics with Weight Loss

Chol ↓ 12% TG ↓ 43%
Insulin ↓ 34%
Adiponectin ↑ 18%

Chan et al. ATVB 2010; 30: 1043-50,
Riches et al. J Clin Endocrinol Metab 1999; 84: 2854-61,
Ng et al. Diabetes Care 30:2945-50,
ApoB and ApoAI Kinetics with Fish Oils

TG ↓ 25%
Apo C-III ➔

28%

AI ↓ 9%
AII ↓ 12%

HDL AI
HDL AII ↓ 9%

49%

13%

Effect of ω-3 Fatty Acid Ethyl Esters on Apolipoprotein B-48 Kinetics in Obese Subjects on a Weight Loss Diet: a New Tracer Kinetic Study in the Postprandial State

Annette TY Wong, Dick C Chan, P Hugh R Barrett, Leon A Adams, Gerald F Watts
ApoB and HDL Particle Kinetics Kinetics with Rosuvastatin

TG ↓ 42%
Apo C-III ↓ 23%
HDL-C ↑ 10%
CETPa ↓ 11%

Asztalos et al  Am J Cardiol 2007; 99: 681-5
Ooi et al  Atherosclerosis 2008; 197: 139-46
Ooi et al  J Clin Endo Metab 2008; 93: 430-37
ApoB and LpAI, LpAI:AII Kinetics with PPAR-α agonist Fenofibrate

TG ↓ 30%
ApoCIII ↓ 30%
ApoCIII FCR ↑ 30%
ApoAII ↑ 23%

Liver

LpAI

LpAI:AII

VLDL

ApoB

IDL

LDL

IDL

LDLr

VLDL

LpAI

LpAI:AII

ApoB48 and ApoB100 Kinetics with Ezetimibe

Chol ↓ 19% TG ↓ 24%
ApoB ↓ 20%

Liver

LDLr

Intestine

Chylo

ApoB48 ↓ 33%

VLDL

ApoB

IDL

23%

20%

28%

17%
ApoB48 and ApoB100 Kinetics with Simvastatin + Ezetimibe

Chol ↓ 43%  TG ↓ 44%
ApoB ↓ 47%

Tremblay et al JLR 2009; 50: 1463-1471
ApoB and ApoAI Kinetics with Niacin ER

HDL-C ↑ 17%
Insulin ↑ 33%

Diabetics on Statin

LDLr

↓ 25%

VLDL

↓ 45%

ApoB

IDL

↑ 20 %

LDL

HDL-AI FCR ↓ 11%

AI ↑ 11%

ApoB and ApoAI Kinetics: CETPI

Non Met S subjects
HDL C ↑ 46%
α1 HDL ↑ 350%
ApoB ↓ 16%

11%

VLDL

ApoB

34%

46%

350%

16%

Augmentation

59%

8%

16%

5%

8%

11%

## Summary: Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>VLDL apoB secretion</th>
<th>ApoB catabolism</th>
<th>ApoB concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt loss</td>
<td>↓</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Fish Oils</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Statin</td>
<td>-</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>CETPI</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>-</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>PPARα</td>
<td>-</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>PPARδ</td>
<td>-</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>PPARγ</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
## Summary: Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>HDL apoA-I concentration</th>
<th>HDL apoA-I catabolism</th>
<th>HDL apoA-I production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt loss</td>
<td>-</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Fish Oils</td>
<td>-</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Statins</td>
<td>-</td>
<td>- or ↓</td>
<td>- or ↓</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CETPi</td>
<td>↑↑↑</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Niacin</td>
<td>↑↑↑</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>PPAR_α</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>PPAR_δ</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PPAR_γ</td>
<td>-</td>
<td>-</td>
<td>-</td>
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Atherogenic Dyslipidaemia in Metabolic Syndrome

Obesity
Insulin resistance
Type 2 Diabetes

Increased CAD Risk

New Approaches to TG Lowering

- Pure EPA esters (Amarin); Free EPA-DHA (Epanova)
- New PPARs: Selective PPAR modulators (K-877); PPAR-α/δ agonist (GFT-505)
- Incretin-based therapies
- ApoB, ApoC-III antisense therapies
- MTP, DGAT-1 inhibitors
- PCSK9 inhibitors

Plasma PCSK9 as a determinant of Apo B-48 catabolism

Chan et al Australian Athero Society Annual Scientific Meeting, Melbourne, Dec 2013
PCSK9 Mab: Effect on Plasma Triglycerides

Baseline TG Subgroup

<table>
<thead>
<tr>
<th>TG ≤150 mg/dL</th>
<th>TG &gt;150 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>N=48</td>
<td>N=27</td>
</tr>
<tr>
<td>150 mg Q2W</td>
<td>150 mg Q2W</td>
</tr>
<tr>
<td>N=66</td>
<td>N=38</td>
</tr>
</tbody>
</table>

Median % change in TG level

- TG ≤150 mg/dL: 2.9% (-23.0, 19.4)
- TG >150 mg/dL: -1.6% (-34.5, 22.3)

-13.9% (-30.1, 6.8)
-26.6% (-44.8, -1.8)

Alirocumab Studies 2013

Study 1003: NCT01266876
Study 11565: NCT01288443
Study 11566: NCT01288469
Conclusions I

- Tracer kinetic studies underpin our understanding of the pathophysiology and therapeutic regulation of dyslipidaemia in the metabolic syndrome.

- TRL transport can be improved by weight loss, exercise, fish oils, statins, PPAR agonists, niacin and CETP inhibitors.

- Weight loss potently decreases hepatic secretion of VLDL; n-3 PUFAs and niacin have weaker, but possibly enhancing effects, on TRL metabolism.

- Decreased catabolism and production of HDL is seen with weight loss, n-3 PUFAs and Rosuvastatin; this cycle may be overcome with fenofibrate.

- PPAR-δ agonists may influence lipoprotein transport by a similar mechanism to Fenofibrate.
The effects of statins on apoB metabolism may be augmented by ezetimibe, n-3 PUFAs, fenofibrate, niacin and CETPIs.

The effects of statins on apoA metabolism may be augmented by fenofibrate, niacin and CETPIs.

There are several new therapies for regulating TRLs that require study.

The CV significance of changes in lipoprotein transport warrants further investigation.