Lipid Disorders in Diabetes (Diabetic Dyslipidemia)

Khosrow Adeli PhD, FCACB, DABCC
Head and Professor, Clinical Biochemistry, The Hospital for Sick Children, University of Toronto
Diabetes – A Global Epidemic

- 2.5% of all deaths globally each year
- 7th leading cause of death by 2030
- 80% of people with diabetes live in low and middle income countries
- Most diabetics are middle-aged (45-64)
- T2DM accounts for 90% of diabetes worldwide
- 50-80% of deaths in diabetics due to cardiovascular disease
- Diabetes deaths likely to double in the next 10 years without urgent action

World Health Organisation, Top 10 Causes of Death Worldwide
Worldwide Incidence of Diabetes over the Last Decade

2013: 347 million

Atkins and Zimmet, NDT 2010
Global Statistics

Prevalence of overweight and obesity in schoolchildren aged 10-16 years, as defined by body mass index, 2001-2

% Prevalence Overweight Children
Source: The International Association for the Study of Obesity

www.yexen.co.uk
Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS
Obesity and Diabetes Are Strongly Linked to Insulin Resistance and Metabolic Complications

Metabolic Syndrome

Hypertension

Dyslipidemia (Metabolic or Diabetic)

Inflammation

Obesity

Coagulation and fibrinolytic abnormalities

Insulin Resistance

Glucose Intolerance

Increased Risk of Type 2 diabetes and Cardiovascular Disease
MRFIT: Cholesterol and CVD Mortality in Men With Type 2 Diabetes

Relation Between Insulin Resistance and Hypertriglyceridemia Established in 1970s

- $r = 0.73$
- $P < 0.0001$

*Total area under 3-hour response curve (mean of 2 tests).*

Common Proatherogenic Features of the Lipid Profile in Diabetic Dyslipidemia

- Elevated TG levels (fasting and post-prandial)
  - Chylos, VLDL, VLDL remnants
- Dense LDL profile
- Elevated ApoB levels
- Low HDL-C levels; Small Dense HDL
- Glycation of apo-B (LDL, Lp(a)) and apo-AI.
- Elevated Lp(a) levels
Insulin resistant patients often have elevated remnants, LDL (increased small dense LDL), and decreased HDL (decreased large alpha 1 HDL).
Diabetic Dyslipidemia involves a disequilibrium characterised by an excess of atherogenic apoB-containing lipoproteins relative to low concentrations of anti-atherogenic HDL whose functional properties are defective.
Characteristic dyslipidemia of insulin resistant states
(Obesity, Type 2 diabetes, Metabolic Syndrome)

- **Low HDL cholesterol**
- **Hypertriglyceridemia**
  - Elevated VLDL
  - Postprandial hyperlipidemia
  - Elevated remnant particles
- **Qualitative LDL particle changes**

<table>
<thead>
<tr>
<th>Insulin sensitive</th>
<th>Insulin resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ TG ↑ HDL-C</td>
<td>↑ TG ↓ HDL-C</td>
</tr>
<tr>
<td>Normal LDL-C</td>
<td>Normal LDL-C</td>
</tr>
<tr>
<td></td>
<td>↑ Dense LDL</td>
</tr>
</tbody>
</table>

Risk of coronary heart disease
Dysfunctional HDL in Type II Diabetes

- ↓ HDL Particle number
- ↑ Small HDL ; ↓ Plasma residence time
- ↓ Transport of antioxidative enzymes

↓ Reverse Cholesterol Transport
↓ Antioxidative protection of LDL
↓ Anti-inflammatory activity

↑ Atherosclerotic Disease
Pathophysiology and Underlying Mechanisms

Tissue and Whole-Body Insulin Resistance
Insulin Resistance & Type 2 Diabetes

Genetic Predisposition &
Overnutrition/Lack of Physical Activity

Overweight/Obesity

Prediabetes/Insulin Resistance

Pancreas

Increased insulin action in more sensitive tissues or biochemical pathways

Tissue Insulin Resistance
Insulin Resistance and Diabetes are Disorders of *Dysregulated Lipid Homeostasis*
Lipid Overflow / Ectopic Fat Model

- Triglyceride surplus deposited in liver, heart, skeletal muscle, & VAT in susceptible subjects (IR, dysfunctional adipose tissue)

Despres and Lemieux, Nature 2006
Fatty Liver/Hepatic Steatosis in Insulin Resistant States

Non-alcoholic Fatty Liver Disease and Cirrhosis

- Simple Fatty Liver (steatosis)
  - Fat accumulates in the liver

- NASH
  - Fat plus inflammation and scarring

- Cirrhosis
  - Scar tissue replaces liver cells

Strongly Associated with:

- Obesity
- Insulin Resistance,
- Type 2 Diabetes,
Diabetic dyslipidemia

- Hypertriglyceridemia
- Reduced HDL-C
- Elevated VLDL
- sdLDL formation
- Elevated chylomicrons
- Elevated chylomicron remnants

Fasting dyslipidemia

- ↓ HDL-C
- ↑ VLDL
- ↑ sdLDL

Postprandial dyslipidemia

- ↑ Chylomicrons
- ↑ Chylomicron remnants

Competition for clearance

Increased risk of atherosclerosis
Mechanisms Relating Insulin Resistance and Dyslipidemia

Fat Cells

\[ \uparrow \text{FFA} \]

Liver

\[ \uparrow \text{FFA} \]

\[ \uparrow \text{VLDL} \]

\[ \uparrow \text{TG} \]

\[ \uparrow \text{ApoB} \]

\[ \downarrow \text{HDLc} \]

\[ \leftrightarrow \text{LDLc} \]

Kidney

Hepatic lipase

\[ \text{ApoA-I} \]

Liver

Insulin lipoprotein lipase

\[ \text{or hepatic lipase} \]

\[ \downarrow \text{LDL} \]

Insulin resistance

Ginsberg HN

While LDLc is similar, particle burden is heavier
Pathophysiology of Dyslipidemia in Type 2 Diabetes

Diabetic Dyslipidemia: Treatment

- Lipoprotein pattern: atherogenic dyslipidemia (high TG, low HDL, small LDL particles)

Therapeutic Management:
- LDL-cholesterol goal: <100 mg/dL
- Baseline LDL-cholesterol ≥130 mg/dL
  - Most patients require LDL-lowering drugs
- Baseline LDL-cholesterol 100–129 mg/dL
  - Consider therapeutic options
- Baseline triglycerides: ≥200 mg/dL
  - Non-HDL cholesterol: secondary target of therapy
Conclusions

Diabetic Dyslipidemia is a common component of the metabolic syndrome and type 2 diabetes.

Lipid Abnormalities are critical underlying factors in insulin resistance and type 2 diabetes.