Metabolic Syndrome: Diabetes/Pre-diabetic state

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Clinical Updates
Topics

• Definitions and criteria: Diabetes, pre-diabetes, and metabolic syndrome
• Atherogenic dyslipidemia
• Pathophysiology of insulin resistance
• Diabetes and ACC/AHA 2013 treatment guidelines
• Residual cardiovascular risk: high TG and low HDL
• Diabetogenicity of statins
Definitions and criteria
Glucose tolerance test (GTT)

- IFG = impaired fasting glucose
- IGT = impaired glucose tolerance

**Normal:**
- FBS <100
- 2 hour <140

**T2D:**
- FBS >125
- 2 hour >200

**IGT:**
- 2 hour 140-200

**IFG:**
- FBS 100-125
## Diagnostic criteria

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pre-diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting BS</td>
<td>&lt;100</td>
<td>100-125</td>
<td>&gt;125</td>
</tr>
<tr>
<td>2-hour BS</td>
<td>&lt;140</td>
<td>140-200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt;5.7</td>
<td>5.8-6.4</td>
<td>&gt;6.5</td>
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</table>
Metabolic syndrome is present if 3 out of 5 diagnostic criteria are present:

- Abdominal obesity: \( \text{waist} > 40” \) (men) or \( 35” \) (women)
- Hypertension: \( \text{BP} > 130/85 \)
- Hypertriglyceridemia: \( \text{TG} > 150 \text{ mg/dl} \)
- Low HDL cholesterol: \( \text{HDL} < 40 \) (men) or \( 50 \) (women)
- Hyperglycemia: \( \text{FBS} > 100 \text{ mg/dl} \)
Metabolic syndrome

**Epidemiology**
- > 50 million in the US have metabolic syndrome
- Prevalence > 30% over age 50

**Risks**
- Risk of diabetes increases 5-fold
- Risks of heart attack and stroke increase 2-fold

**Concept**
- Clustering of risk factors occurs because of shared pathophysiology and mechanisms
Atherogenic dyslipidemia
Atherogenic dyslipidemia

- Elevated TG
- Low HDL
- Small, dense LDL particles
**Atherogenic dyslipidemia**

**Increased VLDL production**
- Increased lipolysis in adipocytes: ↑FFA
- FFA used as substrate to synthesize TG
- FFA block PI3K-dependent degradation of apoB100

**Decreased VLDL clearance**
- Lipoprotein lipase
Atherogenic dyslipidemia

**Less functional HDL**
- TG in VLDL exchanged for cholesteryl esters in HDL by CETP
- TG-enriched HDL, increased clearance

**Atherogenic VLDL**
- Remnant lipoproteins
- Small dense LDL particles
Insulin resistance
Insulin signaling

- Diabetes and metabolic syndrome are associated with *hyperinsulinemia*, to compensate for insulin resistance
- Insulin resistance is *selective*; some signaling pathways are diminished, others are not
- Some disease pathogenesis is because of hyperinsulinemia-driven, unaffected pathways:
  - MAPK vs. Akt in vasculature: more vasoconstriction and less vasodilation
  - Decreased hepatic and skeletal muscle glucose regulation with persistent lipogenesis
Insulin signaling and selective resistance

Diagram showing the pathways involved in insulin signaling and selective resistance.

Muscle and liver pathways are depicted with key molecules such as Akt, SREBP-1c, FOXO1, mTORC1, and eNOS.

Processes include glucose uptake, lipid synthesis, gluconeogenesis, vasoconstriction, and proliferation.

Key points:
- Insulin signaling through the insulin receptor.
- Inhibition of Akt due to selective resistance.
- Pathways leading to glucose uptake, lipid synthesis, and gluconeogenesis.
- Vasoconstriction and proliferation as outcomes.

Institute for Heart, Vascular and Stroke Care.
New targets suggested by pathophysiology

**Targets involved in persistent hepatic lipogenesis**

- mTORC1, which mediates lipogenesis, bypassing normal Akt regulation
- SREPB-1c, transcription factor involved in expression of lipogenic genes

**Targets involved in mitochondrial beta-oxidation**

- Enzymes involved in beta oxidation, such as VLCAD, LCAD are regulated by S-nitrosylation
- Activity of LCAD is regulated by sirtuins
Diabetes and ACC/AHA 2013 treatment guidelines
Four subgroups may benefit from statins:

1. Established ASCVD
2. LDL > 190 mg/dl
3. Ten year risk of ASCVD > 7.5%
4. Type 1 or type 2 diabetes

Concepts

- Paradigm shift away from LDL-based goals
- Risk calculator controversial
Statins reduce CVD in diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>n (T2D)</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Heart Protection Study (HPS)</td>
<td>5963</td>
<td>Simva 40</td>
<td>25% reduction</td>
</tr>
<tr>
<td>Collaborative Atorvastatin Diabetes Study (CARDS)</td>
<td>2800</td>
<td>Atorva 10</td>
<td>37% reduction, early termination</td>
</tr>
<tr>
<td>Atorvastatin Study for Prevention of CHD Endpoints (ASPEN)</td>
<td>2410</td>
<td>Atorva 10</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA)</td>
<td>2226</td>
<td>Atorva 10</td>
<td>25% reduction</td>
</tr>
<tr>
<td>Lescol Intervention Prevention (LIPS)</td>
<td>303</td>
<td>Fluva 80</td>
<td>51% reduction</td>
</tr>
<tr>
<td>Treating to New Targets (TNT)</td>
<td>1501</td>
<td>Atorva 10/80</td>
<td>13.8% vs. 17.9%</td>
</tr>
<tr>
<td>Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)</td>
<td>4162</td>
<td>Prava 40</td>
<td>5.5% absolute RR with atorva 80</td>
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Meta-analysis of statins in diabetes

**Cholesterol Treatment Trials Collaborators**

- Meta-analysis of 14 randomized trials
- \( n = 18,686 \) with diabetes (1466 T1D; 17,220 T2D)
  \( n = 71,370 \) without diabetes
- Mean follow-up 4.3 years
- 9% reduction in all-cause mortality per mM (39 mg/dl) drop in LDL
- 21% reduction in major CVD events per mM drop in LDL
Residual cardiovascular risk: high TG and low HDL
Residual risk associated with HDL and TG

**HDL**

- Epidemiologic studies show HDL is strong, independent inverse predictor of CVD risk
- CETP inhibitor trials show dissociation between HDL raising and CVD reduction
- Functionality of HDL (e.g. reverse cholesterol transport) as well as absolute level of HDL is important

**TG**

- Extreme hypertriglyceridemia is risk for pancreatitis and should be treated
ApoC3, triglycerides, and CHD

**TG and HDL Working Group, NHLBI (n=110,970)**
- identified apoC3 mutations that affect TG levels
- apoC3 loss of function mutations lower TG by 39% and CHD risk by 40%

*NEJM 2014; 371: 22*

**Copenhagen, two studies (total n=75,725)**
- association between TG and CHD risk
- apoC3 loss of function mutations lower TG by 44%, vascular disease by 41%, CHD by 36%

*NEJM 2014; 371: 32*
Niacin

**Effects on lipid profile**
- Lowers TG by 10-30%
- Increases HDL by 10-40%
- Lowers LDL by 5-20%

**Effects on CVD**
- Multiple studies confirm niacin lowers CVD
- Niacin may increase blood glucose levels
- ARBITER: niacin added to statin reduces carotid IMT after 12 months (n=167)
Niacin

AIM-HIGH Study (n=3414, 1/3 with T2D)
- Niacin increased HDL and lowered TG c/w statins alone
- Niacin did not affect CVD endpoint at 2 years
- Study stopped early due to lack of efficacy

*NEJM 2014; 371: 290 and NEJM 2011; 365: 2255*

HPS-2-THRIVE Study (n= 25,673, 1/3 with T2D)
- No reduction in CVD endpoints
- Increased adverse events in niacin group: new diabetes, infection, and bleeding

*NEJM 2014; 371: 203*
Fibrate monotherapy

**Gemfibrozil**
- Monotherapy reduces CVD, including in T2D

**Benzafibrate (BIP Trial)**
- Monotherapy has no benefit on CVD outcome
- No difference in mortality, but reduced endpoints in subgroup with high TG

**Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)**
- Monotherapy reduces total CVD events but not coronary events or mortality
- Benefit greatest in metabolic syndrome and high TG
**ACCORD Study**

- Action to Control Cardiovascular Risk in Diabetes
- Fenofibrate plus simvastatin compared with simvastatin alone
- Primary outcome: nonfatal MI, stroke, or CVD mortality not significantly different
- Prespecified subgroup analysis indicates benefit for
  - men, and
  - those with high TG and low HDL
Diabetogenicity of statins
Statin therapy and risk of T2D

**JUPITER trial**
- Rosuvastatin 20 daily for 1.9 years
- Significant increase 3.0% vs. 2.4% in incident T2D
- Increased A1c

**WOSCOPS trial**
- Pravastatin decreased hazard of T2D by 30%

**Meta-analysis of 13 trials**
- 91,140 patients without diabetes
- 9% increased risk of T2D over 4 years
- Effect is dose related and varies between statins
Statin therapy and risk of T2D
Statins and risk of T2D

• Analysis of risk of developing T2D and CVD risk reduction by statins supports use of statins

• On average, treatment of 255 patients with statins for 4 years results in one additional case of T2D, while preventing 5.4 CVD events in those same 255 patients

• Number needed to harm for intensive-dose statin therapy for one year is 498 for new T2D; number needed to treat is 155 to prevent CVD events

• For new ACC/AHA guidelines, benefits significantly outweigh the risks of developing T2D
Summary and
Take home messages
Summary

- Atherogenic dyslipidemia consists of high TG, low HDL, and small dense LDL particles
- Insulin resistance affects some pathways, but not others
- Statins reduce CVD events in those with T2D (both primary and secondary prevention)
- Residual CVD risk from low HDL or high TG may be treated with fibrates
- Risk of developing T2D from statin is outweighed by benefit of CVD reduction
Take-home messages (1)

**STATINS**
- Statins have been proven to reduce CVD events in T2D
- Risk of developing T2D from statin is outweighed by benefit of CVD reduction

**FIBRATES**
- Fenofibrate added to statin reduces residual CVD risk
- Fibrate monotherapy reduces CVD events in diabetes, especially with high TG and metabolic syndrome
Take-home messages (2)

**NIACIN**

- AIM-HIGH and HSP2-THRIVE
  - did not show further reduction in CVD events when added to statins
  - showed increased adverse events

- Niacin has roles
  - to reduce LDL in statin-intolerant patients
  - to reduce TG in fibrate-intolerant patients
  - in treatment of FH
Discussion