Dyslipidemia in Diabetes

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Outline

• Lipid abnormality in DM

• Pathophysiology of lipid abnormality in DM

• Treatment of dyslipidemia
  – Evidences for drug treatment
  – ADA guideline recommendation
# Lipid Abnormalities in Patients with Diabetes

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1DM</strong></td>
<td>Lipid profile is similar to controls if glycemic control is good</td>
</tr>
<tr>
<td><strong>T2DM</strong></td>
<td>↑TG, VLDL, IDL, and non-HDL-C.</td>
</tr>
<tr>
<td></td>
<td>↓HDL-C (level and function)</td>
</tr>
<tr>
<td></td>
<td>Normal LDL-C but increase in small dense LDL, LDL particle number, and apolipoprotein B.</td>
</tr>
<tr>
<td>Poor</td>
<td>↑TG, VLDL and IDL and</td>
</tr>
<tr>
<td>glycemic</td>
<td>↓HDL-C.</td>
</tr>
<tr>
<td>control</td>
<td>↑LDL-C with increase in small dense LDL and particle number.</td>
</tr>
</tbody>
</table>
Pathophysiology of lipid abnormality in DM

• Increase in Triglycerides
  I. Overproduction
     ➢ Increased fatty acid in the liver
  II. Decreased clearance
     ➢ decrease in lipoprotein lipase activity
        ▪ Decreased Insulin
        ▪ pro-inflammatory cytokines
Three major sources of fatty acids in the liver

• **↑flux of fatty acids from adipose tissue**
  – increased mass of adipose tissue, particularly visceral stores
  – increased triglyceride breakdown due to decrease in insulin or a decrease in insulin activity
  – pro-inflammatory cytokines stimulate lipolysis

• **↑de novo fatty acid synthesis**
  – hyperinsulinemia - liver remains sensitive to the effects of insulin stimulating lipid synthesis
  – hyperglycemia, can induce carbohydrate responsive element binding protein (ChREBP),
  – pro-inflammatory cytokines stimulate de novo FA synthesis
• **↑uptake of triglyceride rich lipoproteins**
  – increase in intestinal fatty acid synthesis and the enhanced secretion of chylomicrons in T2DM.
  – This leads to the increased delivery of fatty acids to the liver.
• **Increased formation and secretion of VLDL**
  – ↓intra-hepatic degradation of Apo B-100
    • High TG
    • Decreased Insulin activity
HDL and LDL

• **Increased production of small dense LDL and small HDL**
  – Increased cholesterol ester transfer protein (CETP) activity due to Hypertriglycerideridemia
  – Increased hepatic lipase activity in T2DM

• **Decreased HDL and decreased affinity of Apo A-I to HDL**
  – accelerated clearance due to small HDL
  – Decreased adiponectin

• **Decreases important functions of HDL, such as its ability to prevent LDL oxidation**
  – Inflammation
Pathophysiology of lipid abnormality in DM
Role of Poor Glycemic Control

- Both T1DM and T2DM
- **Hypertriglyceridemia** and increased synthesis of VLDL → Increase in LDL
- Decreased HDL - small HDL
- Improvements in glycemic control can
  - markedly lower TG levels
  - increase HDL levels
  - lower LDL levels (In very poorly controlled DM)
## Effect of Glucose lowering drugs on lipids

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Modestly decrease triglycerides and LDL-C</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>No effect</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Decrease postprandial triglycerides</td>
</tr>
<tr>
<td>GLP1 analogues</td>
<td>Decrease fasting and postprandial triglycerides</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Decrease triglycerides and increase HDL-C. Small increase LDL-C but a decrease in small dense LDL</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Decrease triglycerides and increase HDL-C. Small increase LDL-C but a decrease in small dense LDL</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Small increase in LDL-C and HDL-C</td>
</tr>
<tr>
<td>Insulin</td>
<td>No effect</td>
</tr>
</tbody>
</table>
Treatment of lipid abnormality

• Lifestyle modification

• Weight loss (if indicated);

• Diet –
  – reduction of saturated fat and trans fat;
  – Increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake;

• Increased physical activity
Epidemiological studies
- increased LDL-C and non-HDL-C levels and decreased HDL-C levels are associated with an increased risk of cardiovascular disease in patients with diabetes.

In the UKPDS cohort
- LDL-C levels were the strongest predictor of coronary artery disease

The role of HDL-C is uncertain

Elevated triglyceride levels play a causal role in atherosclerosis
Statins

- The Cholesterol Treatment Trialists analyzed data from 18,686 subjects with diabetes (mostly T2DM) from 14 randomized trials

- per 39mg/dl reduction in LDL-C
  - ↓ 9% decrease in all-cause mortality
  - ↓13% decrease in vascular mortality
  - ↓21% decrease in major vascular events

- For primary and secondary prevention
Heart Protection study

- Double blind randomized trial
- >20,000 (5963 DM)
- 40 and 80 years of age
- Simvastatin 40mg Vs Placebo
  - ↓27% total cardiovascular disease
  - ↓20% coronary mortality,
  - ↓37% myocardial infarction,
  - ↓24% stroke
- Similar degree benefit in the diabetic subjects
Heart Protection study

- The reduction in cardiovascular events with statin therapy was similar in individuals with:
  - diabetes for <6 years and for >13 years.
  - diabetes in good control (HbA1c <7%) and those not in ideal control (HbA1c >7%)
  - subjects with LDL <120mg/dl benefited to a similar extent as subjects with LDL >120mg/dl
  - T1DM and T2DM patients had a comparable reduction in cardiovascular disease with simvastatin therapy.

➢ The decrease in cardiovascular events in patients with T1DM was not statistically significant because of the small number of subjects.
The Reversal Trial

- 502 symptomatic CAD and an average LDL-C of 150mg/dl.
  - 19% of the patients had diabetes.

- Randomization
  - Pravastatin 40mg OD (moderate) Vs Atorvastatin 80mg (high)

- Pravastatin LDL = 110mg/dl vs. atorvastatin LDL = 79mg/dl

- Atheroma volume determined after 18 months
  - Atorvastatin treated had a much lower progression rate than the group treated with pravastatin.
  - 50% reduction in LDL (LDL-C levels of approximately 75mg/dl) resulted in the absence of lesion progression.
Saturn trial

- Atorvastatin 80mg or Rosuvastatin 40mg would induce regression of coronary artery atherosclerosis to a similar degree in patients with and without diabetes if the LDL-C levels were reduced to less than 70mg/dl

- Asteroid
  - marked reductions in LDL-C (mean LDL-C levels were 61mg/dl) can result in the regression of coronary artery atherosclerosis
FIBRATES- Field Trial

- 9,795 patients with T2DM between the ages of 50 and 75 not taking statin therapy
- randomized to fenofibrate or placebo and
- followed for 5 years.
- Fenofibrate therapy
  - ↓12% LDL-C,
  - ↓29% triglycerides,
  - ↑5% HDL-C levels.
  - ↓11% Coronary events (CHD death and non-fatal MI),
    - *did not reach statistical significance (p= 0.16)*
Monotherapy with fibrates

• The results are not as robust or consistent as seen in the statin trials.

• Fibrate therapy was effective in patients with
  – increased triglyceride levels and decreased HDL levels
NIACIN-Coronary Drug Project

- 1966 to 1974 (before the introduction of statin)
  - ↓15-25% CHD death or nonfatal MI
  - In both DM and non DM
- Niacin reduces insulin sensitivity
  - can worsen glycemic control
  - induced new onset diabetes
- Increase serum uric acid levels and induce gout
- Increased incidence of infection and bleeding
A multicenter, randomized trial in Japan examined the efficacy of ezetimibe in patients aged ≥75 years with elevated LDL-C (≥140 mg/dL) without a history of coronary artery disease who were not taking lipid lowering drugs.

Patients were randomized to ezetimibe (n=1716) or usual care (n=1695) and followed for 4.1 years.

- 25% DM
- ↓34% primary outcome (composite of sudden cardiac death, MI, coronary revascularization, or stroke)
- Both in DM and non DM
<table>
<thead>
<tr>
<th>Effect of Lipid Lowering Drugs</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>↓ 20-60%</td>
<td>↑ 5-15%</td>
<td>↓ 0-35%*</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓ 15-25%</td>
<td>↑ 1-3%</td>
<td>↓ 10-20%</td>
</tr>
<tr>
<td>PCSK9 Inhibitors</td>
<td>↓ 50-60%</td>
<td>↑ 5-15%</td>
<td>↓ 5-20%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓ 0-15%</td>
<td>↑ 5-15%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>↓ 10-30%</td>
<td>↑ 0-10%</td>
<td>↑ 0-10%</td>
</tr>
<tr>
<td>Bempedoic Acid</td>
<td>↓ 15-25%</td>
<td>↓ 5-6%</td>
<td>No change</td>
</tr>
<tr>
<td>High Dose Fish Oil</td>
<td>↑ 0-50%</td>
<td>↑ 4-9%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ 10-25%</td>
<td>↑ 10-30%</td>
<td>↓ 20-50%</td>
</tr>
</tbody>
</table>
**Combination Therapy**

- **STATINS + FIBRATES- ACCORD-LIPID trial**
  - 5,518 T2DM patients on statin therapy were randomized to placebo or fenofibrate therapy.
  - The patients had diabetes for approximately 10 years and either had pre-existing cardiovascular disease or were at high risk for developing cardiovascular disease.
  - LDL-C levels $\approx 80$mg/dl.
  - Mean HDL-C
    - fenofibrate 41.2mg/dl Vs control 40.5mg/dl.
  - Mean triglyceride level
    - fenofibrate 122mg/dl Vs control 144mg/dl.
• For both primary and secondary outcome measures of cardiovascular disease.
  – No statistically significant differences

• Fenofibrate had beneficial effects on the progression of microvascular disease

• Possible benefit of fenofibrate therapy in those with baseline TG >204mg/dl and HDL-C <34mg/dl
STATIN + NIACIN-The AIM-HIGH trial

- Addition of Niaspan to aggressive statin therapy in patients with pre-existing cardiovascular disease
- 3,314 patients and **33% of the patients had diabetes**.
- LDL-C levels were 60-70mg/dl range in both groups.
- HDL-C levels
  - 44mg/dl Niaspan Vs 38mg/dl control
- Triglycerides
  - 121mg/dl Niaspan vs. 155mg/dl control.
- **There were no differences in the primary endpoint**
- May increase the risk of stroke
STATIN + EZETIMIBE-IMPROVE-IT trial

- Ezetimibe to statin therapy in patients with the ACS
- 18,000 patients (27% DM)
- LDL-C levels were 70mg/dl in the statin alone group vs. 53mg/dl in the statin + ezetimibe group.

- ↓6.4% major cardiovascular events in the statin + ezetimibe group (Significant)

- ↓10% CV death, non-fatal MI, or non-fatal stroke

- Beneficial effects were particularly pronounced in the patients with diabetes
Evolocumab vs. placebo in 27,564 patients with atherosclerotic cardiovascular disease and an LDL-C level of 70 mg/dl or higher who were on statin therapy.

- 40% of the patients had diabetes

- Evolocumab treatment significantly reduced the risk of the primary end point by 15% and the key secondary end point by 20%
• A similar decrease in cardiovascular events occurred in patients with diabetes and glycemic control was not altered.

• Similar degree reduction of cardiovascular events in patients with a baseline LDL-C level less than 70mg/dl, as in the patients with an LDL-C greater than 70mg/dl.

• The lower the on-treatment LDL-C levels (down to levels below 20mg/dl), the lower the cardiovascular event rate.

• The ODYSSEY trial – similar positive finding.
STATINS + HIGH DOSE OMEGA-3-FATTY ACIDS-REDUCE-IT Trial

- 2 grams twice per day of EPA ethyl ester (icosapent ethyl) (Vascepa) vs. placebo
- 8,179 patients with hypertriglyceridemia (135mg/dl to 499mg/dl) and established cardiovascular disease or high cardiovascular disease risk (diabetes plus one risk factor) who were on stable statin therapy.
- 60% had diabetes.
- At baseline,
  - median LDL-C was 75.0 mg/dl,
  - HDL-C was 40.0 mg/dl, and
  - Triglyceride was 216.0 mg/dl.
• The median change in TG level from baseline to 1 year
  – decrease of 18.3% (−39.0 mg/dl) in the EPA group and
  – an increase of 2.2% (4.5 mg/dl) in the placebo group

• ↓25% the primary end-point (Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina)

• The beneficial effects were similar in patients with and without diabetes.
• The cardiovascular benefits of EPA were
  – similar across baseline levels of triglycerides (<150, ≥150 to <200, and ≥200 mg/dl).
  – occur irrespective of the attained triglyceride level at 1 year (≥150 or <150 mg/dl),
  – was not associated with attainment of a normal triglyceride level.
  – Multifactorial- decreasing platelet function, anti-inflammation, decreasing lipid oxidation, stabilizing membranes
### Primary Prevention

- **Age 20-39:** With additional risk factors may be reasonable to initiate statin therapy
- **Age 40-75:** Moderate intensity statin therapy
- **Age > 75:** Moderate intensity statin therapy is reasonable after discussion
- **Patients at high risk:** Multiple risk factors*** or age 50-70 it is reasonable to use high intensity statin therapy**
- **Patients with 10-year risk > 20%:** reasonable to add ezetimibe to maximally tolerated statin to reduce LDL by > 50%

### Secondary Prevention

- **All ages < 75:** High intensity statin therapy/maximally tolerated statin
- **Age >75:** Reasonable to continue statin therapy or initiate statin therapy after discussion.
- **Very High Risk:** If LDL > 70mg/dl on maximally tolerated statin consider adding ezetimibe or PCSK9 inhibitor
Treatment of hypertriglyceridemia

• For patients with fasting TG >500 mg/dL,

• Evaluate for secondary causes
  – Chronic liver and kidney disease and/or nephrotic syndrome
  – Hypothyroidism

• Consider medical therapy to reduce the risk of pancreatitis.
  – fibric acid derivatives or fish oil
• Moderate hypertriglycerideremia (175–499 mg/dL),
  – address and treat lifestyle factors (obesity and metabolic syndrome),
  – Secondary factors and medications that raise TG

• In patients with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL),
  – Addition of icosapent ethyl can be considered to reduce cardiovascular risk
Take home message

• First priority in treating lipid disorders in patients with diabetes lower the LDL-C levels to goal.

• Dietary therapy is the initial step but, in almost all patients, will not be sufficient to achieve the LDL-C goals.

• Statins are the first-choice drugs to lower LDL-C levels
• If a patient is unable to tolerate statins or statins as monotherapy are not sufficient

  – second-choice drug is either ezetimibe or a PCSK9 inhibitor.

  – Bile acid sequestrants and bempedoic acid are alternatives with the use of a bile acid sequestrant particularly useful if a reduction in A1c level is also needed
• The second priority should be non-HDL-C (non-HDL-C = total cholesterol – HDL-C), which is particularly important in patients with elevated triglyceride levels (>150mg/dl).

• To lower triglyceride levels initial therapy should focus
  – Glycemic control and lifestyle changes including a decrease in simple sugars and ethanol intake.
  – Discontinue medications that increase triglyceride levels.
  – Fibrates and omega-3-fatty acids reduce triglyceride levels.
• Patients with very high TG (> 500-1000 mg/dl)
  – risk of pancreatitis
  – lifestyle and triglyceride lowering drug therapy
  – Fenofibrate or omega-3-fatty acids

• No clinical trials demonstrating that increasing HDL-C levels reduce cardiovascular disease.

• Use of drugs such as niacin to raise HDL-C levels is not recommended.