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

T1DM	Lipid profile is similar to controls if glycemic control is good
T2DM	↑TG, VLDL, IDL, and non-HDL-C. ↓ HDL-C (level and function) Normal LDL-C but increase in small dense LDL, LDL particle number, and apolipoprotein B.
Poor glycemic control	↑TG, VLDL and IDL and ↓HDL-C. ↑LDL-C with increase in small dense LDL and particle number.

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

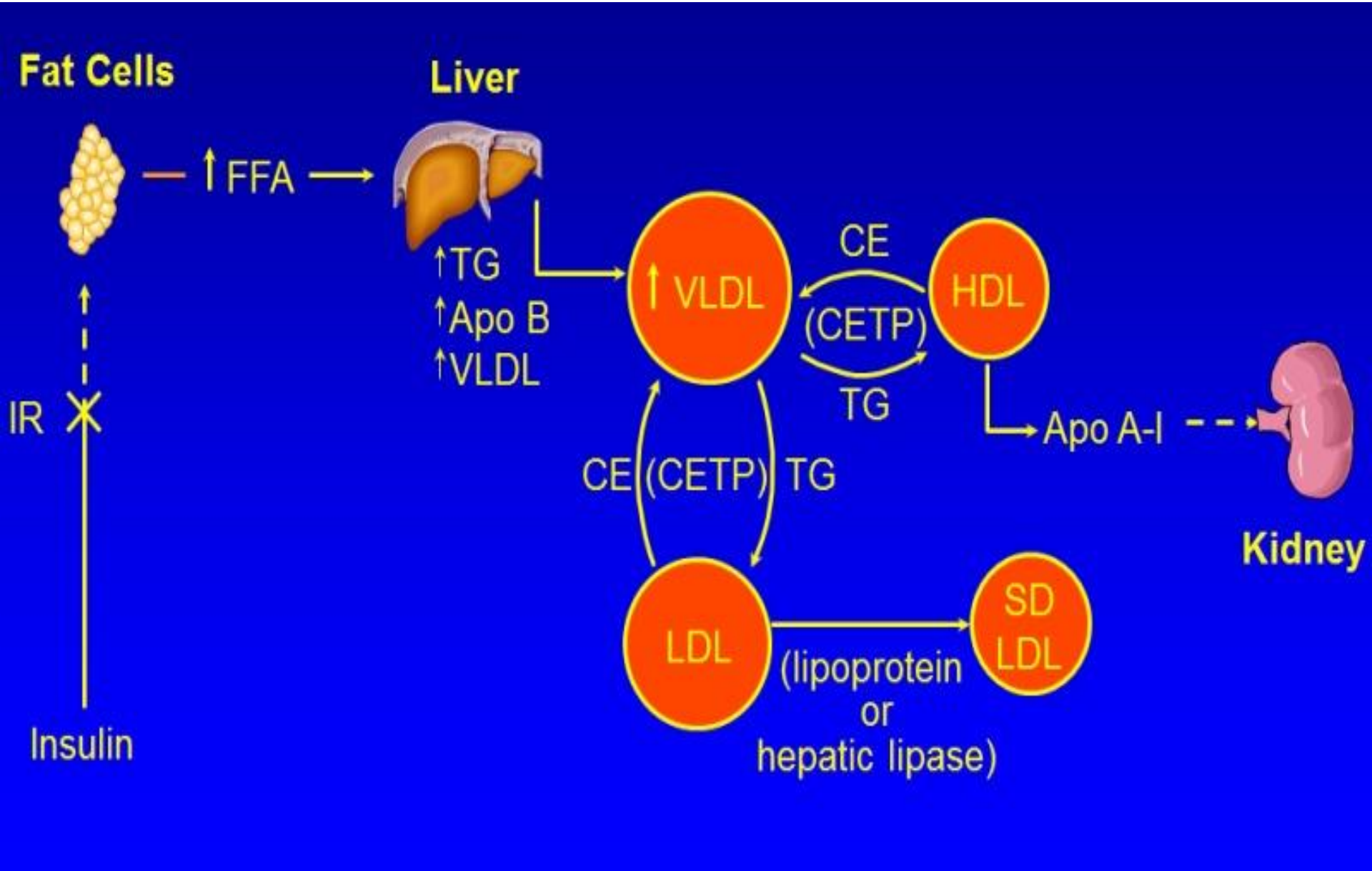
- **↑uptake of triglyceride rich lipoproteins**
  - increase in intestinal fatty acid synthesis and the enhanced secretion of chylomicrons in T2DM.
  - This leads to the increased delivery of fatty acids to the liver.

- **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 Hypertriglyceridemia
  - 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

Metformin	Modestly decrease triglycerides and LDL-C
Sulfonylureas	No effect
DPP4 inhibitors	Decrease postprandial triglycerides
GLP1 analogues	Decrease fasting and postprandial triglycerides
Pioglitazone Rosiglitazone	Decrease triglycerides and increase HDL-C. Small increase LDL-C but a decrease in small dense LDL
SGLT2 inhibitors	Small increase in LDL-C and HDL-C
Insulin	No effect

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**

Lipid lowering drugs- Benefits

- 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

EZETIMIBE

- 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

Effect of Lipid Lowering Drugs

	LDL-C	HDL-C	TG
Statins	**↓ 20-60%**	↑ 5-15%	↓ 0-35%*
Ezetimibe	↓ 15-25%	↑ 1-3%	↓ 10-20%
PCSK9 Inhibitors	**↓ 50-60%**	↑ 5-15%	↓ 5-20%
Fibrates	↓ 0-15%	↑ 5-15%	**↓ 20-50%**
Bile acid sequestrants	↓ 10-30%	↑ 0-10%	↑ 0-10%
Bempedoic Acid	↓ 15-25%	↓ 5-6%	No change
High Dose Fish Oil	↑ 0- 50%	↑ 4- 9%	**↓ 20- 50%**
Niacin	↓ 10-25%	**↑ 10-30%**	↓ 20-50%

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 ≈ 80mg/dl.
  - Mean HDL-C
    - fenofibrate41.2mg/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**

STATIN + PCSK9 INHIBITORS-The FOURIER trial

- 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 stain
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 hypertriglyceridemia (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.