

OVERVIEW OF LIPID METABOLISM

Date: September 20, 2005 *
Time: 8:00 am- 8:50 am *
Room: G-202 Biomolecular Building
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*Please consult the online schedule for this course for the definitive date and time for this lecture.

Office Hours: by appointment

Assigned Reading: This syllabus.

Key Concepts vs Supplementary Information: Because this syllabus is meant to replace the need for a Biochemistry textbook, it contains a mixture of information that is critical for you to know and information that serves to illustrate and explain the key points. I have attempted to emphasize important terms, definitions and concepts in **red**, and have listed **key points** after each section of the syllabus. In this section, some key points from your lectures on carbohydrate metabolism are shown in **blue**. *Illustrative and supplementary information is indicated in italics.*

OVERALL GOALS OF THIS SECTION: You should:

1. Understand how lipid metabolism normally responds in the fed state, the fasting state, and during exercise.
2. Understand how lipid metabolism is altered in patients with metabolic syndrome and/or diabetes.

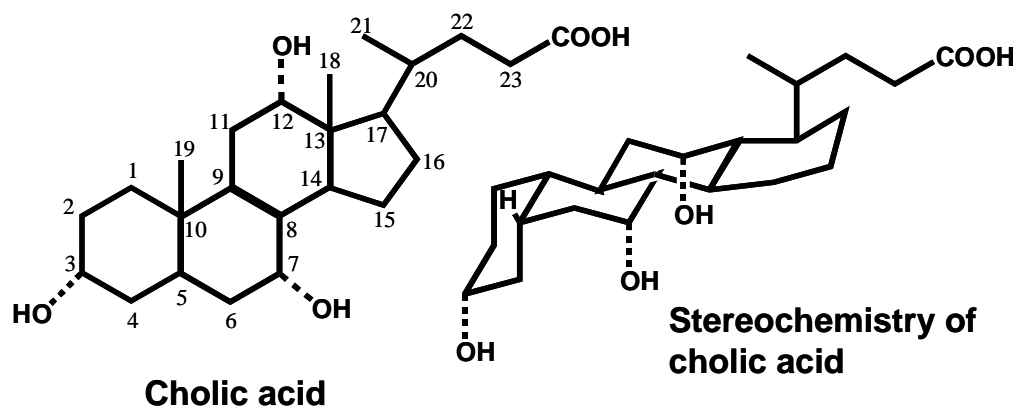
Lecture Objectives: At the conclusion of this lecture you should know:

- 1) How fats, cholesterol and fat-soluble vitamins are digested and absorbed
- 2) How lipid metabolism is controlled in the fed state, the fasting state and during exercise.
- 3) How the control of lipid metabolism is altered with metabolic syndrome and diabetes

A. Digestion of Lipids

1. Emulsification of Fats

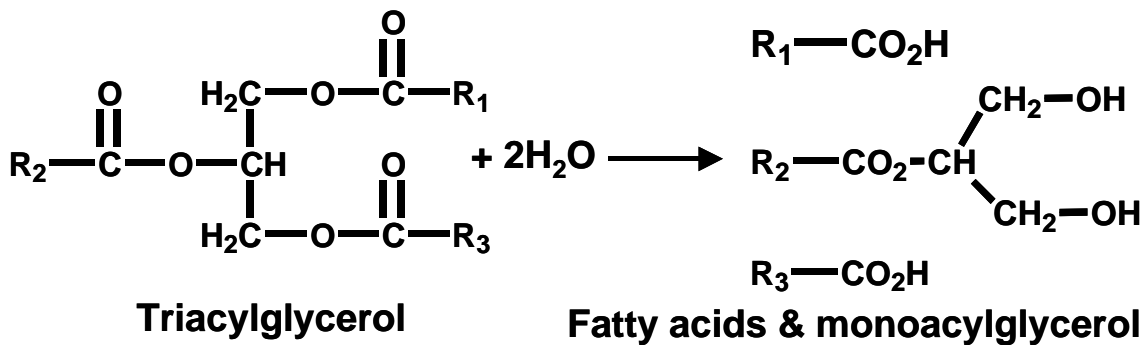
Fatty acids can be liberated by simple hydrolysis of the ester bonds in triglycerides, but the **insolubility of the triglycerides presents a problem**; digestion occurs following dispersion of dietary fat into small particles with sufficiently exposed surface area for rapid attack by digestive enzymes. This is achieved by detergent action and mechanical mixing, with the **detergent effect** being supplied by several components, both in the diet and in the digestive juices, but especially by partially digested fats (fatty acid soaps and monacylglycerols) and by **bile salts**.



The bile salts such as cholic acid contain a hydrophobic side and a hydrophilic side, thus allowing bile salts to dissolve at an oil-water interface, with the hydrophobic surface in contact with the nonpolar phase and the hydrophilic surface in the aqueous medium. This detergent action **emulsifies fats and yields mixed micelles, which allow attack by water-soluble digestive enzymes** and facilitate the absorption of lipids through the intestinal mucosa. **Mixed Micelles also serve as transport vehicles for those lipids that are less water-soluble than fatty acids, such as cholesterol or the fat-soluble vitamins A, D, E, and K.** Thus, efficient absorption of lipids depends on the presence of sufficient bile acids to solubilize the ingested lipids.

2. Digestion of Fats.

The emulsification of fats render them susceptible to hydrolysis by enzymes secreted by the pancreas. The most important enzyme involved is **pancreatic lipase**. *Pancreatic lipase is virtually specific for the hydrolysis of primary ester linkages, the 1 or the 3 ester bonds, but not the bond in the central 2 position (see below). As a result of this conversion, 2-monoglycerides (2-monoacylglycerols) are major end-products of triglyceride digestion.* Less than 10% of triglycerides remain unhydrolyzed in the intestine.



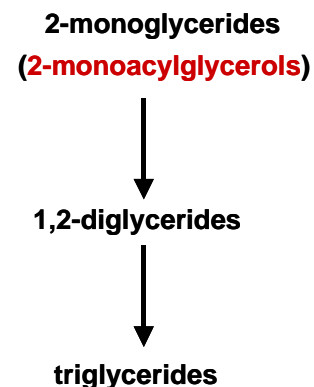
3. Control of Fat Digestion

Initial products of digestion (e.g., free fatty acids) stimulate release by the duodenum of the 33 amino acid peptide hormone **pancreozymin-cholecystokinin (PZ-CCK)**. The **cholecystokinin (CCK)** activity induces **emptying of the gallbladder**, thus leading to **increased concentration of bile salts** and other bile constituents **in the intestine**, including cholesterol and phospholipids. The **pancreozymin (PZ)** activity causes **release of pancreatic digestive enzymes, including pancreatic lipase**.

B. Absorption of Lipids

Short-chain fatty acids (up to 12 carbons) are absorbed directly through the villi of the intestinal mucosa. They enter the blood via capillaries that eventually **empty into the portal vein and are transported** via lipid carrier proteins **directly to the liver**, where they are used for energy production. **2-Monoglycerides, long-chain fatty acids (more than 12 carbons), cholesterol and lysophospholipids are absorbed from the lumen by intestinal mucosal cells, where they are incorporated into lipoproteins and directed to the lymphatic system.**

Within the intestinal wall, the triglycerides are resynthesized by the 2-monoacylglycerol pathway as shown on the right. The 2-monoacylglycerol pathway is unique for the intestine. Triglycerides, having been synthesized in the intestinal mucosa, are not transported to any extent in the portal venous blood. Instead, **the great majority of absorbed lipids, including triglycerides, phospholipids, cholesterol esters, and cholesterol, appear in the form of chylomicrons that pass to the lymphatic vessels of the abdominal region and later to the systemic blood** (see Lipoprotein Metabolism).

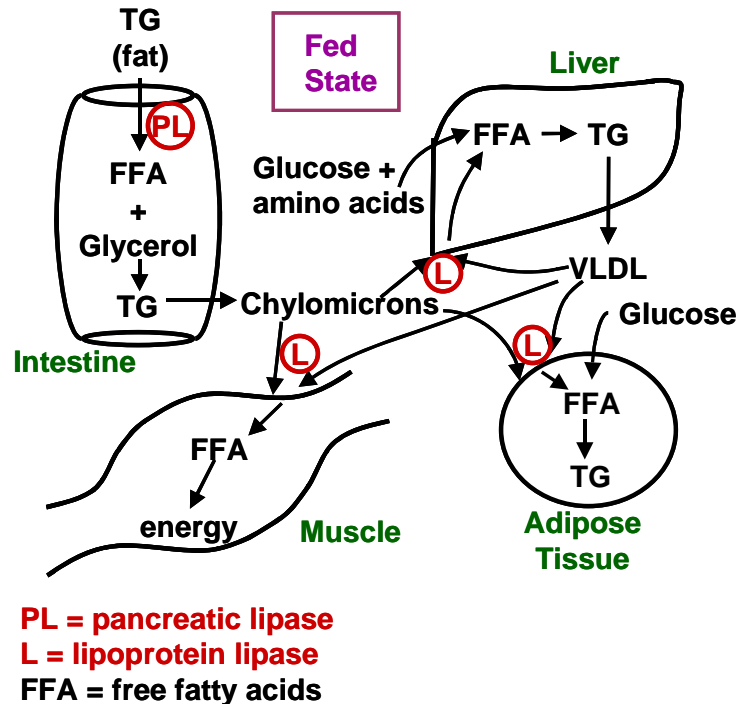


KEY POINTS: DIGESTION AND ABSORPTION OF LIPIDS

- 1) **Bile salts** help in the digestion of fats, cholesterol and fat-soluble vitamins by forming **mixed micelles** which solubilize the fats and render them accessible to digestive enzymes.
- 2) The presence of free fatty acids in the duodenum causes release of the peptide hormone **pancreozymin-cholecystokinin** which causes the **gallbladder** to release **bile salts** and the pancreas to release **pancreatic lipase**.
- 3) **Pancreatic lipase** hydrolyzes triglycerides (triacylglycerols) to give **free fatty acids** and *2-monoglycerides* which are absorbed by the intestinal mucosa cells.
- 4) **Short-chain fatty acids** ($\leq C12$) enter the portal vein and are transported directly to the liver.
- 5) All other fatty acids are re-esterified with the 2-monoglycerides to form **triglycerides** which are incorporated into lipoprotein particles called **chylomicrons** which enter the **lymphatic vessels**.

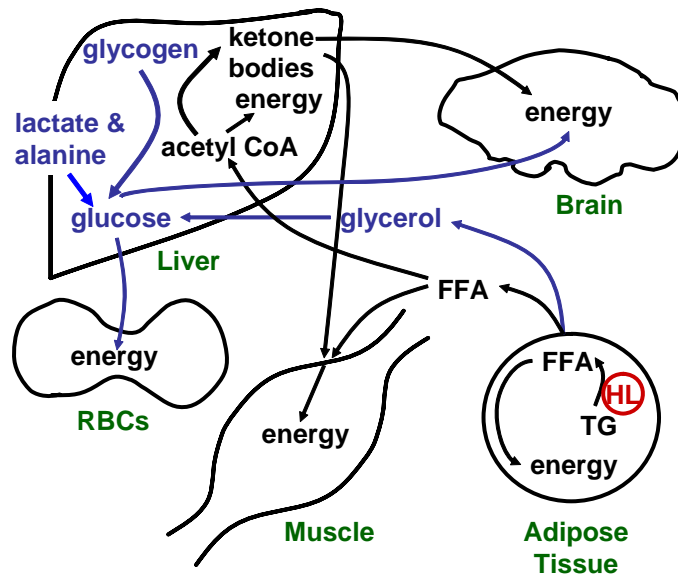
C. Overview of Lipid Metabolism in Fed State, Fasting State & Exercise

Overview of Fatty Acid Metabolism



Lipid Metabolism in the Fed State (animation found in PowerPoints)

- 1) **Dietary fat (triglyceride) is hydrolyzed to free fatty acids and glycerol (actually monoacylglycerol) in the intestine by pancreatic lipase (PL).**
- 2) Short chain fatty acids can enter the circulation directly, but most **fatty acids are reesterified with glycerol in the epithelial cells of the intestine. The resulting triglycerides enter the circulation as lipoprotein particles called chylomicrons through the lymphatic system.**
- 3) **The triglycerides in chylomicrons can be cleared by lipoprotein lipase (L) at the endothelial surface of capillaries. The resulting fatty acids can be: a) stored as fat in adipose tissue (Note: Triglycerides (fat) can also be made from excess glucose in the fed state); b) used for energy in any tissue with mitochondria and an ample supply of O₂ (Note: Most tissues will be relying on glucose as their primary energy source in the fed state. The exception would be exercising muscle); and c) reesterified to triglycerides in the liver and exported as lipoproteins called VLDL. (Note: Triglycerides and VLDL can also be synthesized from excess glucose and amino acids in the liver during the fed state).**
- 4) **VLDL has essentially the same fate as the chylomicrons.**
- 5) **Insulin stimulates lipoprotein lipase. It also stimulates fatty acid and triglyceride synthesis in liver and adipose tissue and inhibits hormone-sensitive lipase in the adipose tissue.**



Lipid Metabolism During Fasting & Exercise (animation found in PowerPoints)

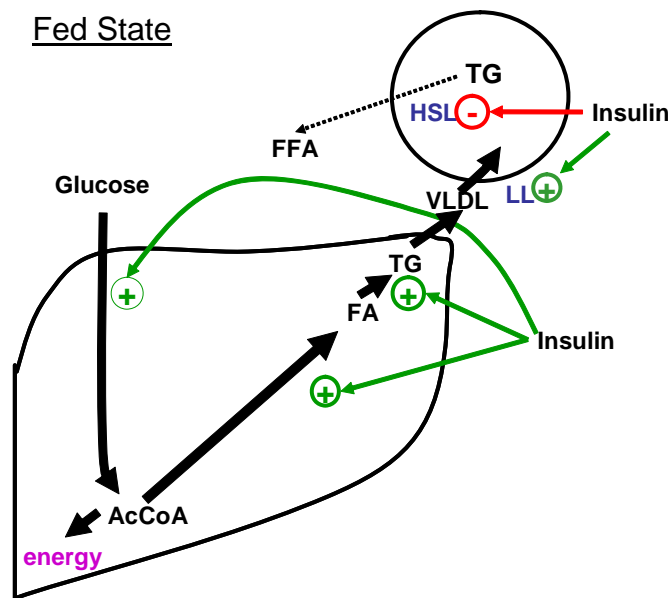
- 1) Glycogen breakdown provides glucose and protein breakdown provides alanine, which is converted to glucose in the liver. The blood glucose is used by the brain and red blood cells. Most other tissues, including resting muscle, are relying primarily on fatty acids as an energy source. Exercising muscle will use both fatty acids and glucose for energy. The relative contribution these energy sources depends on the intensity of the exercise.
- 2) **Hormone-sensitive lipase** is activated by **glucagon** (fasting) or **epinephrine** (exercise). Therefore, **fat in adipose tissue is hydrolyzed to give glycerol and fatty acids during both fasting and exercise.**
- 3) **The fatty acids can be used directly as an energy source by most tissues with mitochondria, excluding the brain (Why?).**
- 4) The glycerol can be converted to glucose in the liver. This is a minor source of glucose.
- 5) **Glucagon & epinephrine stimulate hormone-sensitive lipase and inhibit lipoprotein lipase, fatty acid synthesis and triglyceride synthesis**
- 6) **During prolonged starvation, the fatty acids can also be converted to ketone bodies in the liver.** These ketone bodies can be used as an **energy source by all tissues** except those lacking mitochondria (eg. red blood cells). **Brain adapts slowly to the use of ketone bodies during prolonged starvation.**

D. Control of VLDL Levels in Health and Disease

- 1) **The liver normally synthesizes fat and exports it as VLDL particles only in the fed state.**

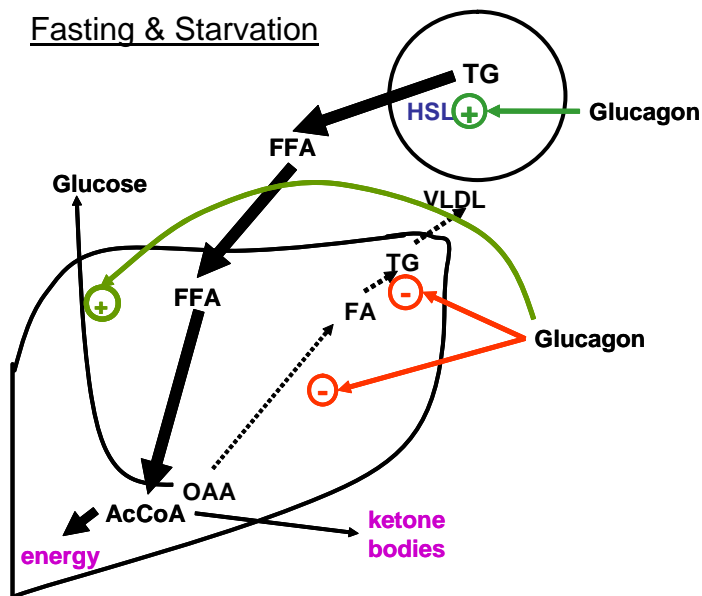
- 2) However, when tissues become **insulin resistant** (metabolic syndrome & type 2 diabetes), **VLDL levels are often higher than normal. This is often coupled with lower than normal HDL levels, a condition called dyslipidemia.**

Let's start with a brief overview of how the adipose tissue and liver interact to regulate VLDL levels in the normal state (fed & fasting) and in the abnormal state (metabolic syndrome & diabetes). You'll learn more about the mechanisms of these effects in the next two lectures.



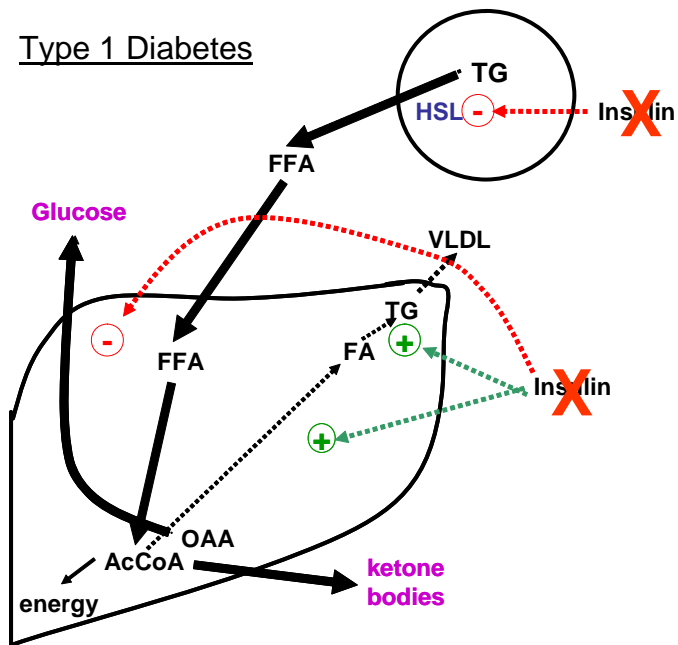
Overview of Fatty Acid Metabolism in the Fed State (animation in PowerPoints)

- o **Insulin inhibits hormone-sensitive lipase (HSL).** No fatty acids are released from the adipose tissue
- o **Insulin stimulates glycolysis and inhibits gluconeogenesis in the liver.** Some of the acetyl CoA is used for energy.
- o **Insulin stimulates fatty acid and triglyceride synthesis in the liver.** The triglycerides made in the liver are exported as VLDL.
- o **Insulin stimulates lipoprotein lipase (LL).** Fatty acids are removed from VLDL and stored in the adipose tissue.



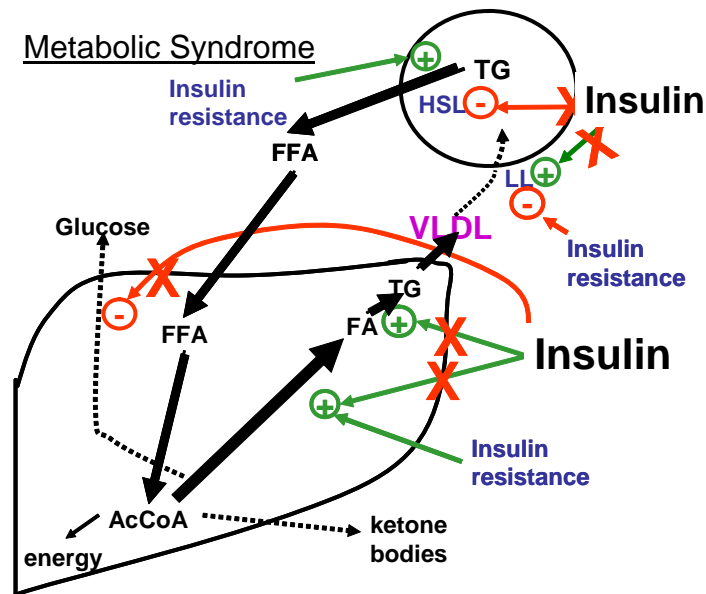
Overview of Fatty Acid Metabolism During Fasting & Starvation (animation in PowerPoints)

- **Glucagon activates hormone sensitive lipase (HSL). Fatty acids are released** from adipose tissue
- **Mass action drives β -oxidation** in the liver. **Acetyl CoA is produced.**
- **Glucagon inhibits fatty acid and triglyceride synthesis**
- **Most of the acetyl CoA enters the C.A.C. and is used for energy production.**
- **As glycogen stores are depleted and gluconeogenesis depletes OAA levels, acetyl CoA cannot be used by the mitochondria and ketone body production becomes more prominent.**



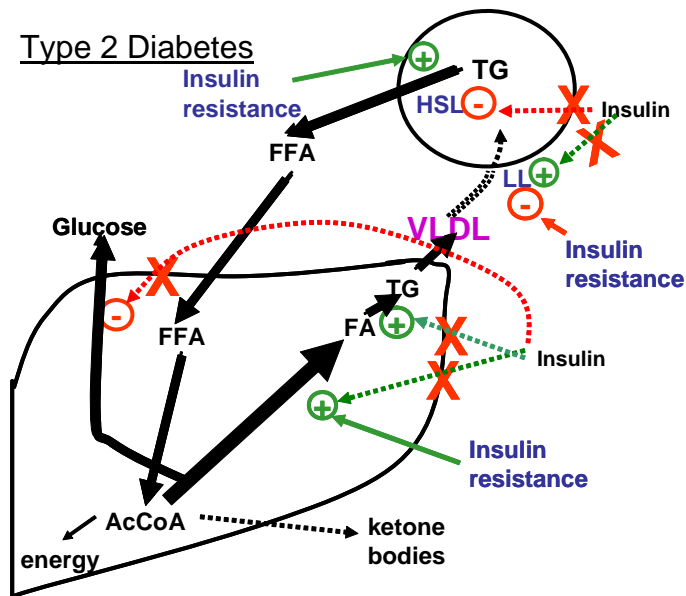
Overview of Fatty Acid Metabolism in Type 1 Diabetes (animation in PowerPoint)

- Because insulin is not produced, it cannot inhibit lipolysis and gluconeogenesis. It is also unable to stimulate fatty acid synthesis.
- Therefore, **lipid metabolism behaves as if the body were undergoing prolonged starvation** (even though blood glucose levels are high) and ketone body synthesis can become excessive.
- **The net result is hyperglycemia and ketonemia.**



Overview of Fatty Acid Synthesis in Metabolic Syndrome (animation in PowerPoints)

- **Tissues are insulin resistant, but insulin is overproduced.** Thus, many reactions controlled by insulin operate normally. Gluconeogenesis is inhibited and fatty acid synthesis is stimulated.
- However, **insulin resistance causes hormone sensitive lipase to be activated.** Thus, **high levels of free fatty acids are released by the adipose cells.**
- **Mass action drives β -oxidation in the liver,** causing an accumulation of acetyl CoA.
- **Both insulin and the insulin resistance itself drive fatty acid and triglyceride synthesis in the liver.**
- **Insulin resistance causes lipoprotein lipase to be inhibited.**
- The **net effect is an accumulation of triglyceride-rich VLDL particles.** This and the accompanying decreased HDL levels are referred to as **dyslipidemia** and are characteristic of the **metabolic syndrome.**



Overview of Fatty Acid Metabolism in Type 2 Diabetes (animation in PowerPoint)

- The **pancreas can no longer produce enough insulin to overcome resistance**, so **most tissues behave as if insulin were absent. Thus, gluconeogenesis increases.**
- Because the adipose cells are insulin resistant, **hormone-sensitive lipase is activated and free fatty acid levels increase even more.**
- **Mass action still drives β -oxidation**, which causes an accumulation of acetylCoA.
- Because gluconeogenesis is active, you would normally expect ketogenesis, but **the insulin resistance still drives fatty acid and triglyceride biosynthesis in the liver.**
- The net result is a combination of hyperglycemia and dyslipidemia