## CHAPTER 3: Complications of Obesity

#### Part 2: Dyslipidemia

References:

- 1. Obesity Medicine Association, & National Lipid Association. (2024). Obesity, dyslipidemia, and cardiovascular disease: A joint expert review from the Obesity Medicine Association and the National Lipid Association. Obesity Pillars. <u>https://doi.org/10.1016/j.obpill.2024.100108</u>
- 2. Dyslipidemia: <u>https://www.ncbi.nlm.nih.gov/books/NBK560891/</u>

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#### Outline

- 1. Overview of Dyslipidemia
- 2. Obesity and Dyslipidemia

# Part 1: Overview of Dyslipidemia

### What is Dyslipidemia?

- Abnormal levels of lipids in the bloodstream, which poses a significant risk factor for cardiovascular diseases (CVDs).
- Diagnosis often relies on lipid profile tests, with recommended target levels for optimal CV health.
- It usually does not cause any symptoms, but it can be detected by a blood test.



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#### Lipid Profile

- Optimal levels according to <u>the CDC</u>:
  - Total cholesterol: About 150 mg/dL
  - LDL cholesterol: 100 mg/dL or below
  - HDL cholesterol: At least 40 mg/dL in men and 50 mg/dL in women
  - Triglycerides: Less than 150 mg/dL
- The relationship between HDL and total cholesterol is also a predictor of CVD risk
  - Ideal is <3.5, but the normal range is <5</li>

## Types of Dyslipidemia: Primary

Caused by genetic mutations that affect the metabolism of lipids. Examples:, familial hypertriglyceridemia, and familial combined hyperlipidemia

- Familial hypercholesterolemia: caused by mutations in the LDL receptor gene (*recall LDL receptor*)
- Familial hypertriglyceridemia: caused by mutations in the LPL gene, which impair the hydrolysis of triglycerides in chylomicrons and VLDL. (*recall LPL*)
- Familial combined hyperlipidemia: caused by the overproduction of VLDL and LDL by the liver, leading to high cholesterol and

triglyceride levels and insulin resistance.

#### Recall: LDL Receptor



Figure 18.20 STUDENTS-HUB.com

## Recall: Lipoprotein Lipase (LPL)



## Types of Dyslipidemia: Secondary

Caused by lifestyle factors or other medical conditions that alter the levels of lipids in the blood.

This is reversible or modifiable by addressing the underlying cause. Examples:

- Obesity: Increased production of VLDL and decreased liver clearance of chylomicrons.
- Diabetes mellitus: Insulin resistance → impairing triglyceride lipolysis and the uptake of LDL cholesterol.
- Hypothyroidism: Decreased expression of LDL receptors and lipoprotein lipase.
- Alcohol abuse: Increased synthesis of VLDL and decreased oxidation of fatty acids by the liver.
- Smoking: Impair the function and synthesis of HDL cholesterol.
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## Pathophysiology

Dyslipidemia can cause:

- Inflammation: Elevated levels of LDL and triglyceride-rich lipoproteins promote their retention in arterial walls → development and progression of atherosclerosis. (*recall atherosclerosis*)
- Cardiovascular Diseases: Dyslipidemia can increase the risk of cardiovascular diseases, such as coronary artery disease, stroke, and heart failure, by promoting atherosclerosis and its complications.

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#### **Recall: Atherosclerosis**



Monocytes—phagocytic white blood cells—circulate in the bloodstream and respond to injury on the artery wall. Monocytes slip under blood vessel cells and engulf LDL cholesterol, becoming foam cells. The thin layers of foam cells that develop within artery walls are known as fatty streaks. A fatty streak thickens and forms plaque as it accumulates additional lipids, smooth muscle cells, connective tissue, and cellular debris.

The artery may expand to accommodate plaque. When this occurs, the plaque that develops often contains a large lipid core with a thin, fibrous covering and is vulnerable to rupture and thrombosis.

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# Part 2: Obesity and Dyslipidemia

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#### Introduction

Obesity is associated with increased CVD risk,

substantially *due to worsening of CVD risk factors* 

 An adiposopathic dyslipidemia pattern is described in patients with obesity, and is likely to contribute to a higher CVD risk

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## Lipid profile in patients with obesity

A common clinical lipid profile pattern associated with obesity includes:

- Elevated blood triglyceride levels due to elevated triglyceriderich lipoproteins
- Reduced HDL-C, reduced apoA-I (i.e., reflecting a decrease in HDL particle concentration)
- Elevated non-HDL-C, elevated apoB, and increased proportion of small dense LDL particles with an increase in LDL particle concentration

### Lipid profile in patients with obesity



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## Recall: Apo1A and ApoB



#### Small dense LDL particles



Lipoprotein Level in Newly Diagnosed Type 2 Diabetes Mellitus Patients With Normal Low-Density Lipoprotein. Cureus 15(1): e33924. DOI 10.7759/cureus.33924

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Variable	Study (n = 50)	Control (n = 50)	P-value
	Median (first quartile-third quartile)	r-value	
Total cholesterol (mg/dL)	174.5 (165.75-185.75)	173 (161-188.25)	0.95
Triglyceride (mg/dL)	105 (93-105.25)	104 (94-145)	0.65
HDL-C (mg/dL)	42 (39-45)	44 (39-46)	0.27
LDL-C (mg/dL)	109.9 (99.4-119.4)	108.5 (87.55-124.1)	0.94
sdLDL-C (mg/dL)	40.11 (36.28-43.58)	24.64 (22-32.49)	<0.0001*

#### TABLE 2: Blood lipid parameters in the study and control groups

#### newly diagnosed T2DM patients compared to age and sex-matched controls.

Juhi A, Jha K, Mondal H (January 18, 2023) Small Dense Low-Density Lipoprotein Level in Newly Diagnosed Type 2 Diabetes Mellitus Patients With Normal Low-Density Lipoprotein. Cureus 15(1): e33924. DOI 10.7759/cureus.33924



#### 300 participants with different BMI

Atherogenic sdLDL-cholesterol and resistin association with vitamin B12 in relation to Body Mass Index. Fauzia Ashfaq, Jwaher Haji Alhaji, Mohammed, Salem Alharbi, Fahmida Khatoon, Nayef Hamad E Alhatlani, Fahad Ayash Mari Alkhamisi, Ghareeb O. Alshuwaier, Mohammad Idreesh Khan, Mirza Masroor Ali Beg. doi: https://doi.org/10.1101/2024.01.08.24300967

## Dyslipidemia in Obesity

- Dyslipidemia in obesity may occur due:
  - 1. Insulin Resistance
  - 2. Adiponectin and TNF Levels

#### 1. Insulin resistance

- Among those with obesity, the responsiveness of LPL to insulin and feeding may be relatively decreased
- LPL activity may be inadequate to fully hydrolyze the obesity-related increase in circulating triglyceride-rich lipoproteins → Elevated triglyceride levels

Let's look at this closer in the following figures:

#### Insulin and LPL



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### IR and LPL



High-Density Lipoprotein as a Key Component in the Prevention of Premature Atherosclerotic Disease in the Insulin Resistance Syndrome. June 2004. Seminars in Vascular Medicine 4(2):215-23. DOI: 10.1055/s-2004-835381. Boris Hansel, Anatol Kontush, and Marcel Twickler Ploaded By: anonymous

#### 1. Insulin resistance

- The main consequences of IR that contribute to hypertriglyceridemia include:
  - Impaired suppression of lipolysis in adipocytes → increased release of FFA that are delivered to the liver
  - 2. Impairment of LPL activity

#### 1. Insulin resistance

- In obesity, there is an increased triglyceride-rich lipoprotein production and decreased triglyceride-rich lipoprotein lipolysis.
- Impairment of fat storage in dysfunctional adipocytes during positive caloric balance → increases circulating fatty acids that flux to the liver → Increased hepatic
   VLDL production → Increased circulating blood triglyceride levels.

#### 2. Role of Adiponectin and TNF-alpha

• Recall: How are their levels changed in obesity?

	Obese State	Lean State	Effect on insulin sensitivity	
	Levels			
Adipokines				
Leptin	Ŷ	$\downarrow$	Deficiency of leptin or its receptor leads to obesity and insulin resistance	
Adiponectin	$\downarrow$	<b>↑</b>	Low adiponectin concentrations are associated with reduced insulin sensitivity	
Resistin	↑	$\downarrow$	Possible link between high resistin levels and insulin resistance	
TNF-alpha	Ŷ	$\downarrow$	TNF-alpha decreases insulin signaling and increases serum-free fatty acids	
IL-6	↑	$\downarrow$	IL-6 decreases insulin signaling and adiponectin secretion	
PAI-1	↑	$\downarrow$	Possible link between high PAI-1 levels and insulin resistance	

Table 7-1 Level of different adipokines in lean and obese individuals, and their effect on insulin sensitivity

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#### Role of Adiponectin

- Adiponectin enhances LPL activity → Catabolism of triglyceriderich lipoproteins → decrease in blood triglyceride levels.
- Decreased Adiponectin levels in obesity → ??

- An increase in pro-inflammatory cytokines secretion stimulates the production and delays the clearance of triglyceride-rich lipoproteins.
  - Tumor necrosis factor stimulate lipolysis in adipocytes → Increase circulating FFA levels → Increases the delivery for hepatic triglyceride synthesis → increased production and secretion of VLDL.

#### Obesity and HDL-C levels

- Low blood HDL-C levels are associated with increased CVD risk.
- Blood levels of HDL-C are largely dependent on an individual's genetic predisposition, nutrition, and physical activity.
- What factors lead to lower HDL levels in obesity? (see next slide)

