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DISORDERS OF LIPID DIGESTION AND ABSORPTION: LIPOPROTEIN METABOLISM, PATHOPHYSIOLOGICAL MECHANISMS, AND CLINICAL IMPLICATIONS

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Abstract: Lipids are essential biomolecules that serve as major sources of energy, structural components of cellular membranes, and precursors of biologically active compounds. Efficient digestion, absorption, transport, and metabolism of lipids are fundamental for maintaining metabolic homeostasis. Lipid digestion involves coordinated actions of bile acids, pancreatic enzymes, intestinal epithelial cells, and lipoprotein transport systems. Disturbances in these processes may result in lipid malabsorption, nutritional deficiencies, dyslipidemia, and increased risk of cardiovascular and metabolic diseases. Lipoproteins play a crucial role in the transport of triglycerides, cholesterol, phospholipids, and fat-soluble vitamins throughout the body. Abnormalities in lipoprotein metabolism contribute significantly to atherosclerosis, coronary artery disease, obesity, and metabolic syndrome. This review discusses the physiological mechanisms of lipid digestion and absorption, causes and consequences of malabsorption disorders, lipoprotein metabolism, and their clinical significance. Recent advances in molecular biology and lipidomics have enhanced understanding of lipid-related disorders and opened new avenues for diagnosis and therapeutic intervention.

Keywords: Lipid digestion, lipid absorption, lipoproteins, dyslipidemia, malabsorption syndrome, cholesterol metabolism, atherosclerosis.

Introduction

Lipids are among the most important biological molecules necessary for normal cellular and systemic function. They provide energy, maintain membrane integrity, participate in signal transduction, and serve as precursors for steroid hormones and bioactive mediators.[1,2,3,4]

Unlike carbohydrates and proteins, lipids are hydrophobic molecules that require specialized mechanisms for digestion, absorption, and transport. The gastrointestinal tract, liver, pancreas, lymphatic system, and vascular network work together to ensure efficient lipid utilization.[5,6,7,8]

Disruption of any stage of lipid metabolism can lead to serious pathological consequences. Disorders of lipid digestion and absorption may result in malnutrition and vitamin deficiencies, whereas abnormalities in lipoprotein metabolism are strongly associated with cardiovascular disease and metabolic dysfunction.[9,10,11,12]

Physiological Basis of Lipid Digestion

Lipid digestion is a multistep process involving mechanical, chemical, and enzymatic mechanisms.

Dietary lipids consist primarily of:





Triglycerides

Phospholipids

Cholesterol esters

Fat-soluble vitamins

Approximately 90–95% of dietary lipids are triglycerides.

Gastric Phase of Lipid Digestion

Although lipid digestion occurs predominantly in the small intestine, the stomach initiates this process.[13,14,15,16]

Gastric Lipase

Gastric lipase hydrolyzes triglycerides into:

- Diglycerides
- Free fatty acids

This phase is particularly important in infants because milk fat digestion begins in the stomach.

Mechanical mixing also contributes to emulsification of lipid droplets.

Intestinal Digestion of Lipids

The majority of lipid digestion occurs in the duodenum and jejunum.

Role of Bile Acids

Bile acids synthesized from cholesterol are secreted into the small intestine.

Functions include:

Emulsification of dietary lipids

Formation of micelles

Increased accessibility of lipids to digestive enzymes

Without adequate bile secretion, lipid digestion becomes significantly impaired.[17,18,19,20]

Role of Pancreatic Enzymes

Several pancreatic enzymes participate in lipid digestion.

Pancreatic Lipase

Hydrolyzes triglycerides into:

Monoglycerides

Free fatty acids

Phospholipase A2

Digests phospholipids.

Cholesterol Esterase

Hydrolyzes cholesterol esters and fat-soluble vitamin esters.

These enzymes are essential for efficient intestinal absorption.

Lipid Absorption Mechanisms

Following digestion, lipid products form mixed micelles.

Micelles facilitate transport of:

Fatty acids

Monoglycerides

Cholesterol



Fat-soluble vitamins
to the intestinal epithelial surface.

Within enterocytes:

Lipids are absorbed.

Triglycerides are resynthesized.

Lipoprotein particles are assembled.

The resulting chylomicrons enter lymphatic vessels and subsequently reach systemic circulation.[21,22,23,24]

Disorders of Lipid Digestion and Absorption

Defects in digestion and absorption lead to malabsorption syndromes.

These conditions result in inadequate uptake of dietary lipids and fat-soluble vitamins.

Pancreatic Insufficiency

Pancreatic exocrine dysfunction reduces secretion of digestive enzymes.

Common causes include:

Chronic pancreatitis

Cystic fibrosis

Pancreatic cancer

Pancreatectomy

Consequences include:

Steatorrhea

Weight loss

Nutritional deficiencies

Bile Acid Deficiency

Reduced bile acid availability impairs emulsification.

Causes include:

- Liver disease
- Biliary obstruction
- Gallstone disease
- Ileal resection

Patients often develop impaired absorption of vitamins A, D, E, and K.

Intestinal Disorders

Diseases affecting intestinal mucosa interfere with lipid absorption.[25,26,27,28]

Examples include:

Celiac disease

Crohn's disease

Tropical sprue

Short bowel syndrome

Damage to enterocytes reduces absorptive capacity.

Genetic Disorders

Several inherited diseases affect lipid transport and absorption.

Abetalipoproteinemia

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Caused by mutations affecting microsomal triglyceride transfer protein.

Clinical manifestations include:

- Severe fat malabsorption
- Neurological dysfunction
- Retinal degeneration

Chylomicron Retention Disease

Characterized by impaired chylomicron secretion from enterocytes.

Affected individuals develop growth retardation and vitamin deficiencies.[29,30,31]

Clinical Consequences of Lipid Malabsorption

Persistent lipid malabsorption produces numerous complications.

Nutritional Consequences

Weight loss

Protein-energy malnutrition

Growth retardation

Vitamin Deficiencies

Vitamin A Deficiency

Night blindness

Visual impairment

Vitamin D Deficiency

Osteomalacia

Rickets

Vitamin E Deficiency

Neurological dysfunction

Vitamin K Deficiency

Bleeding disorders

Early diagnosis is essential to prevent irreversible complications.

Lipoprotein Metabolism

Because lipids are insoluble in water, specialized transport systems are required.

Lipoproteins are macromolecular complexes composed of:

- Lipids
- Apolipoproteins
- Phospholipids
- Cholesterol

These structures transport lipids through the bloodstream.

Classification of Lipoproteins

Lipoproteins are classified according to density.

Chylomicrons

Largest and least dense lipoproteins.

Functions:

Transport dietary triglycerides

Deliver lipids from intestine to tissues

Very-Low-Density Lipoproteins (VLDL)



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Synthesized in the liver.

Functions:

Transport endogenous triglycerides

Intermediate-Density Lipoproteins (IDL)

Represent transitional particles formed during VLDL metabolism.

Low-Density Lipoproteins (LDL)

Major carriers of cholesterol.

Functions:

Deliver cholesterol to peripheral tissues

Elevated LDL levels are strongly associated with atherosclerosis.

High-Density Lipoproteins (HDL)

Functions:

Reverse cholesterol transport

Removal of excess cholesterol from tissues

High HDL concentrations generally confer cardiovascular protection.

Apolipoproteins and Their Functions

Apolipoproteins regulate lipoprotein metabolism.

Important examples include:

ApoA-I

Major structural protein of HDL.

ApoB-100

Required for LDL formation and receptor binding.

ApoB-48

Essential for chylomicron assembly.

ApoC-II

Activates lipoprotein lipase.

ApoE

Mediates lipoprotein clearance by the liver.

Defects in apolipoproteins contribute to dyslipidemia.

Metabolism of Chylomicrons

Chylomicrons transport dietary lipids from the intestine.

Following entry into circulation:

1. ApoC-II activates lipoprotein lipase.
2. Triglycerides are hydrolyzed.
3. Fatty acids enter adipose tissue and muscle.
4. Chylomicron remnants are removed by the liver.

This pathway is essential for utilization of dietary fats.

VLDL and LDL Metabolism

The liver synthesizes VLDL particles containing triglycerides and cholesterol.

During circulation:

Triglycerides are removed.

VLDL becomes IDL.



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IDL is converted to LDL.

LDL delivers cholesterol to tissues through receptor-mediated endocytosis.

Excessive LDL accumulation promotes atherogenesis.

HDL Metabolism and Reverse Cholesterol Transport

HDL plays a central role in cholesterol homeostasis.

Functions include:

Collection of excess cholesterol

Transport to the liver

Promotion of cholesterol excretion

HDL also possesses:

Antioxidant activity

Anti-inflammatory properties

Endothelial protective effects

These characteristics contribute to cardiovascular protection.

Disorders of Lipoprotein Metabolism

Abnormal lipoprotein metabolism leads to dyslipidemia.

Common disorders include:

Familial Hypercholesterolemia

Caused by LDL receptor mutations.

Features:

Markedly elevated LDL cholesterol

Premature cardiovascular disease

Familial Combined Hyperlipidemia

Characterized by elevated:

LDL

Triglycerides

It is among the most common inherited lipid disorders.

Hypertriglyceridemia

Associated with:

Obesity

Diabetes mellitus

Alcohol abuse

Severe cases may cause acute pancreatitis.

Lipoproteins and Cardiovascular Disease

Atherosclerosis remains the leading cause of cardiovascular mortality worldwide.

Pathogenesis involves:

1. LDL infiltration into arterial walls.
2. Oxidative modification.
3. Macrophage activation.
4. Foam cell formation.
5. Plaque development.

Protective HDL functions oppose these processes.



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The balance between atherogenic and antiatherogenic lipoproteins significantly influences cardiovascular risk.[32,33,34]

Modern Advances in Lipid Research

Recent developments have improved understanding of lipid metabolism.

Key innovations include:

Lipidomics

Genomic profiling

PCSK9 inhibitors

RNA-based therapeutics

Precision medicine

These advances provide new opportunities for personalized treatment of lipid disorders.[35,36]

Conclusion

Lipid digestion, absorption, and transport are highly coordinated physiological processes essential for maintaining metabolic homeostasis. Disorders affecting these mechanisms result in malabsorption syndromes, nutritional deficiencies, and systemic complications. Lipoproteins serve as indispensable carriers of lipids throughout the body, and abnormalities in their metabolism contribute significantly to cardiovascular and metabolic diseases. Advances in molecular biology and clinical lipidology continue to improve understanding of these disorders and support the development of innovative therapeutic strategies aimed at reducing disease burden and improving patient outcomes.

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