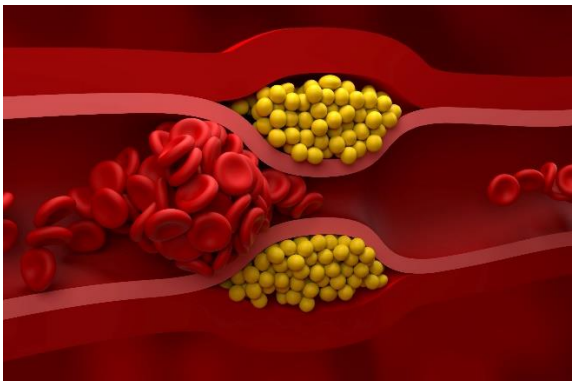
On Metabolic Health Effects of Lipoproteins

A recent study published provides a comprehensive review of the lipoprotein pathway in healthy metabolism.



Lipoproteins

Lipoproteins consist of lipids that are chemically attached to protein conjugates called apolipoproteins. These amphipathic molecules have a central lipid core of cholesterol esters and triacylglycerol within a double membrane of phospholipids and free cholesterol conjugated to apolipoproteins.

Some examples of lipoproteins include high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and lipoprotein(a) (LP[a]), with the density of these molecules inversely related to their size. HDL and LDL are the smallest lipoproteins at eight to 12 nanometers (nm) and 18-25 nm, respectively, whereas chylomicrons are the largest at 100-1200 nm.

Dietary lipids are digested within the gastrointestinal tract, following which they enter the intestinal mucosa to become chylomicrons, transporting triacylglycerols from food into the blood. Chylomicron breakdown in muscle or fat tissue yields chylomicron remnants for excretion by liver cells.

Lipoprotein synthesis occurs in the liver and begins with the production of VLDL, which contains triglycerides. After further processing, these triglycerides become intermediate-density lipoproteins (IDL) and, subsequently, LDL or LP(a).

VLDL transports triacylglycerols produced by the body, whereas LDL delivers cholesterol from the liver to other tissues. LDL initiates atherosclerotic plaque formation and, as a result, is a biomarker for cardiovascular disease (CVD) risk. HDL carries cholesterol from peripheral tissues to the liver through reverse cholesterol transport (RCT).

Lipoprotein synthesis is followed by its secretion into the bloodstream, transportation, modification, and elimination from the body. Liver cells and macrophages acquire lipoproteins through endocytosis to either break down or use these molecules.

Lipoproteins and CVD

The primary route of blood LDL management is by macrophage uptake of cholesterol esters. Within the macrophage, cholesterol esters are eventually converted to foam cells, which serve as free cholesterol for storage or exit the cell through transporters.

In addition to high cholesterol levels and reduced migration of macrophage foam cells, high LDL worsens atherosclerosis, which is exacerbated by genetic and metabolic factors. Increased oxidized LDL 1 (LOX-1) expression can lead to plaque instability, thrombosis, and acute CVD.

Atherosclerosis also triggers inflammation due to the activation of pattern-recognition receptors by oxidative stress. These effects are particularly evident among obese individuals, as well as those of an older age and diabetics.

Oxidized LDL can lead to leukocyte adhesion, activate apoptosis, and cause endothelial dysfunction. Additionally, it increases collagen synthesis and cell proliferation by fibroblasts and vascular smooth muscle cells.

Atherogenic dyslipidemia is common in obesity and increases the risk of diabetes mellitus and CVD. Although HDL levels are low in both obesity and diabetic dyslipidemia, triglyceride-rich lipoproteins like LDL are high.

Dyslipidemia Management

Dyslipidemia increases the risk of CVD, particularly in the presence of type 2 diabetes, as well as tumor development and neurodegenerative diseases like Alzheimer's dementia. Dyslipidemia can also lead to high cholesterol levels, obesity, atherosclerosis, inflammation, and insulin resistance.

Importantly, both genetic and dietary factors affect the incidence of dyslipidemia. For example, chylomicron storage disease and abetalipoproteinemia can interfere with lipid absorption.

Although many risk factors for dyslipoproteinemia are unmodifiable, such as aging, sex, ethnic origin, or familial diseases caused by genetic mutations, various new therapies are being investigated. Gene therapy, for example, offers a promising approach to modifying the pathogenic genes involved in the development of dyslipidemia. Recent animal studies have produced promising results in utilizing gene-editing technologies to reduce circulating LDL and protein convertase subtilisin/kexin type 9 (PCSK9) levels.

PCSK9 is an enzyme that promotes clotting, leukocyte recruitment, and platelet activation within the bloodstream, thereby promoting CVD progression and affecting LDL receptor availability. PCSK9 antibodies, including alirocumab, evolocumab, and the ribonucleic acid (RNA) molecule inclisiran, have been shown to reduce LDL levels.

Statins inhibit cholesterol synthesis, reducing LDL levels, whereas ezetimibe and fibrates inhibit lipid absorption.

Novel anti-diabetic therapies, including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1Ra (GLP-1Ra) agonists, and GLP-1 and glucose-dependent insulinotropic peptide (GIP) dual receptor agonists, have also been found to effectively manage dyslipidemia. These drugs can be used with or without lipid-lowering agents, which may support the optimization of treatment schedules, improve patient compliance, and lead to better outcomes.

The relationship between lipid metabolism and microbes in the gut lumen is an emerging field of research that may also lead to the development of new therapies.

RCT is a potential treatment approach for CVD; however, no data is available to support the correlation between HDL and CVDs. Apolipoprotein E (apoE) is also key to RCT, as it contributes with apoB to LDL removal. ApoE analogs offer another route to enhance RCT and prevent atherogenesis.

Source:

https://www.news-medical.net/news/20240711/How-lipoproteins-shape-your-metabolic-health.aspx