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REVIEW ARTICLE

Hypercholesterolemia As a Risk Factor for Cardiovascular Disease: Current Controversial Therapeutic Management

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Cholesterol is a precursor of steroid hormones and an essential component of the cell membrane; however, altered regulation of the synthesis, absorption and excretion of cholesterol predispose to cardiovascular diseases of atherosclerotic origin. Despite the recognition of historical events for 200 years starting with Chevreul naming ''cholesterine''; later on, Lobstein coining the term atherosclerosis and Marchand introducing it, Anichkov identifying cholesterol in atheromatous plaque, and Brown and Goldstein discovering LDL receptor (r-LDL), as well as the emergence of different drugs such as fibrates, statins and cetrapibs during this decade promising to increase HDL, and the most recent, ezetimibe and anti-PCSK9 to inhibit the degradation of r-LDL, morbidity has not been reduced in cardiovascular disease. To date, the controversy continues regarding the best and appropriate medical therapy for hypercholesterolemia; likewise, there is the recommendation of a healthy dietary content regarding the amount of sugar as well as the type of fats, either saturated or polyunsaturated. Together, control of circulating cholesterol, amelioration of hypertension, regulation of diabetes, and dietary recommendations might prevent atherosclerosis.

Key Words: Hypercholesterolemia, Lipoproteins, Atherosclerosis, Cardiovascular disease, Statins.

Introduction

Cholesterol (from the Greek chole: bile, and stereos: solid) is followed by the suffix ''ol'', which means organic alcohol is a sterol molecule. Thus, the modified steroid is biosynthesized by all animals including humans because it is an essential component of the cell membrane that provides fluidity and motility as well as functional and metabolic regulation. The hydroxyl group on cholesterol interacts with the polar head groups of the membrane phospholipids, whereas the bulky steroids and the hydrocarbon chain are embedded in the membrane alongside the nonpolar fatty acid chain of the other lipids (Figure 1).

In addition, cholesterol is the precursor for the biosynthesis of vitamin D, all steroid hormones and bile acids (1–3). The major production of cholesterol takes place in the liver by the hepatocytes and transferred into the circulatory system to be distributed by several lipoproteins in the whole body. Because cholesterol is essential for all animal life, each cell synthesizes it through a complex 37-step process beginning with the mevalonate pathway and ending with a 19-step conversion of lanosterol to cholesterol (Figure 2). A human male weighing 70 kg synthesizes about 900 mg/day, and his body contains about 35 g, mostly located within the cell membranes. Moreover, daily cholesterol dietary intake is ~307 mg; therefore, ingested cholesterol has little effect on circulating cholesterol because it is poorly absorbed and immediately esterified. This explains the reason that high animal food intake does not result in high cholesterol values in all persons. Moreover, cholesterol ingestion, although transported in extracellular water within lipoproteins, does not significantly alter lipoprotein concentrations such as carbohydrates commonly do (4–6).

Transport of Cholesterol

Cholesterol in food, 7–10 h after ingestion, has little, if any, effect on concentrations of cholesterol in the blood.

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Figure 1. Eminent researchers in cholesterol study. Eugene Chevreul named cholesterine (later named cholesterol) from gallstones. Felix Marchand coined the term atherosclerosis. Adolf Windaus worked on the constitution of sterols and their connection with vitamins. Nikolai Anichkov discovered the significance and role of cholesterol in atherosclerosis pathogenesis. John Gofman identified and distinguished the three major classes of plasma lipoproteins. Akira Endo developed statin drugs. Julies Hirsh established the biological underpinnings of obesity. Brown and Goldstein discovered lipoprotein receptors, mainly low-density.

The liver excretes it in a non-esterified form into the digestive tract, typically ~50% of the excreted cholesterol is reabsorbed by the bowel back into the bloodstream. As an isolated molecule, cholesterol is only minimally soluble in water. It dissolves into the bloodstream only at exceedingly small concentrations. Phospholipids and cholesterol, being amphipathic, are transported in the monolayer surface of the lipoprotein particle (7). There are several types of lipoprotein in the blood in order of increasing density. These are chylomicrons, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) (4). Lipoprotein particles are organized by complex apolipoproteins, which can be recognized and bound by specific receptors on cell membranes, directing their lipid payload into specific cells and tissues currently ingesting these fat transport particles. Chylomicrons carry fast from the intestine to muscle and other tissues in need of fatty acids for energy or fat production. In addition, unused cholesterol remains as cholesterol-rich chylomicron remnants and taken up from here to the bloodstream by the liver. These molecules contain apolipoprotein B100 and apolipoprotein E in their shells and are degraded by apolipoprotein lipase on the blood vessel wall. LDL particles are the major blood cholesterol carriers to be oxidized and taken up by macrophages, which become engorged and form foam cells. These foam cells often become trapped in