

LIVER IN LIPOPROTEIN METABOLISM

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Liver plays a major role in cholesterol and lipoprotein metabolism and is the major site of production and removal of cholesterol rich lipoproteins and bile acids. In addition, liver secretes enzymes such as hepatic lipase, lecithin cholesterol acyl transferase (LCAT) and cholesterol ester transfer protein (CETP) which are required for lipoprotein metabolism. Hepatocellular injury and cholestasis have major effects not only on the concentration and Composition of plasma lipoproteins but also on their inherent structural properties¹.

Plasma lipoproteins serve three major functions:

- (1) they deliver triglyceride derived fatty acids from the liver and intestine to muscle and adipose tissue,
- (2) cholesterol to tissues that require it and
- (3) return excess cholesterol to the liver².

Lipoproteins on the basis of their function are classified as very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). Transportation of triglyceride from the intestine and liver is achieved by chylomicrons and very low density lipoprotein. Although most cells are able to synthesize cholesterol, low density lipoprotein is utilized to deliver cholesterol to tissues that require it, while the return of excess cellular cholesterol to the liver is mediated by HDL in a process which involves the passive transfer of membrane cholesterol to HDL, its conversion to cholesterol esters and its ultimate transfer to LDL and the liver. Each of these functions depends on the presence of specific apolipoprotein, as essential cofactors or as receptor binding sites³. The intestine and liver each assemble, synthesize and secrete triglyceride-rich lipoproteins and high density lipoproteins. VLDL is the major triglyceride rich lipoprotein secreted by the liver and has to cope with rapid changes in intracellular triglyceride levels. When an imbalance occurs between hepatic triglyceride synthesis and VLDL synthesis, triglyceride accumulates within hepatocytes, resulting in fatty liver⁴. VLDL secretion is dependent on the concentration of free fatty acid in the hepatocyte and on the metabolic state of the liver. Variation in hepatic triglyceride synthesis depend on the extent to which FFA are oxidized to CO₂ and ketone bodies. Fasting, low insulin, glucagon, cAMP and cGMP accelerate ketogenesis. Conversely feeding insulin and oestrogens stimulate triglyceride synthesis and VLDL secretion⁵. Chylomicrons are the intestinal equivalent of VLDL. When dietary fat is ingested, the intestinal mucosa absorbs the digestive products (FFA, monoglycerides, cholesterol and lysolecithin) and resynthesizes triglycerides, phospholipids and cholesterol esters. Absorbed cholesterol is esterified and is the major source of chylomicron cholesterol esters. The liver and intestine secrete high density lipoprotein (HDL) as biliary discs⁶. Secretion of HDL appears to be independent of VLDL secretion but is dependent on the expression of apolipoproteins which itself is regulated by diet, oestrogen, thyroid hormone, phenobarbital and during development⁷⁻¹². Lipoprotein catabolism is a dynamic process. Newly secreted hepatic and intestinal lipoproteins are rapidly modified in a process which involves continual interactions with existing lipoproteins. Lipoprotein lipase hydrolyses triglycerides located within the core of triglyceride-rich lipoproteins and forms free fatty acid and monoglycerides¹³. After lipolysis a chylomicron remnant is released into the circulation. Like chylomicron VLDL are modified as soon as they enter the blood stream. After hydrolysis the end product of lipoprotein lipase action is the intermediate density lipoprotein (IDL), a VLDL remnant. In humans, about half of all IDL particles are removed by the liver and those which are not removed from circulation are quantitatively converted to LDL, the end product of VLDL metabolic cascade. Approximately 75% of LDL is

removed from circulation by the liver and most of this is mediated by the LDL receptor pathway¹⁴. In this context, liver plays a dominant role because of its large size. A decrease in LDL receptors causes an increase in the production of LDL as well as a decrease in its removal from the blood¹⁵. It is perhaps unfortunate that when: LDL receptors are most needed to remove excess LDL from the circulation, the hepatocyte is most likely to suppress LDL receptor levels in an effort to protect itself from an overdose of plasma derived cholesterol². The normal regulatory mechanism can be utilized clinically to create a demand for cholesterol and to increase the number of hepatic LDL receptors. Bile acid binding resins prevent the absorption of bile acids by the intestine and deplete the liver of bile acids. The liver responds by synthesizing bile acids which in turn leads to a demand for cholesterol which is satisfied in part by an increased number of LDL receptors. Plasma LDL cholesterol levels drops by 15-20% as a result. The use of HMG CoA reductase inhibitors inhibits cholesterol biosynthesis with a resultant increase in the number of LDL receptors. This has two major effects: (i) it increases the uptake of LDL from circulation, which results in a net decrease in the production of LDL and (ii) it increases the uptake of LDL from an already diminished pool. Treatment with such inhibitors decreases plasma LDL - cholesterol levels by 20-40%¹⁶.

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