AIN SHAMS UNIVERSITY
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"MODERN VIEW IN HYPERLIPIDEMIA

An Essay Submitted for the Partial Fullfilment
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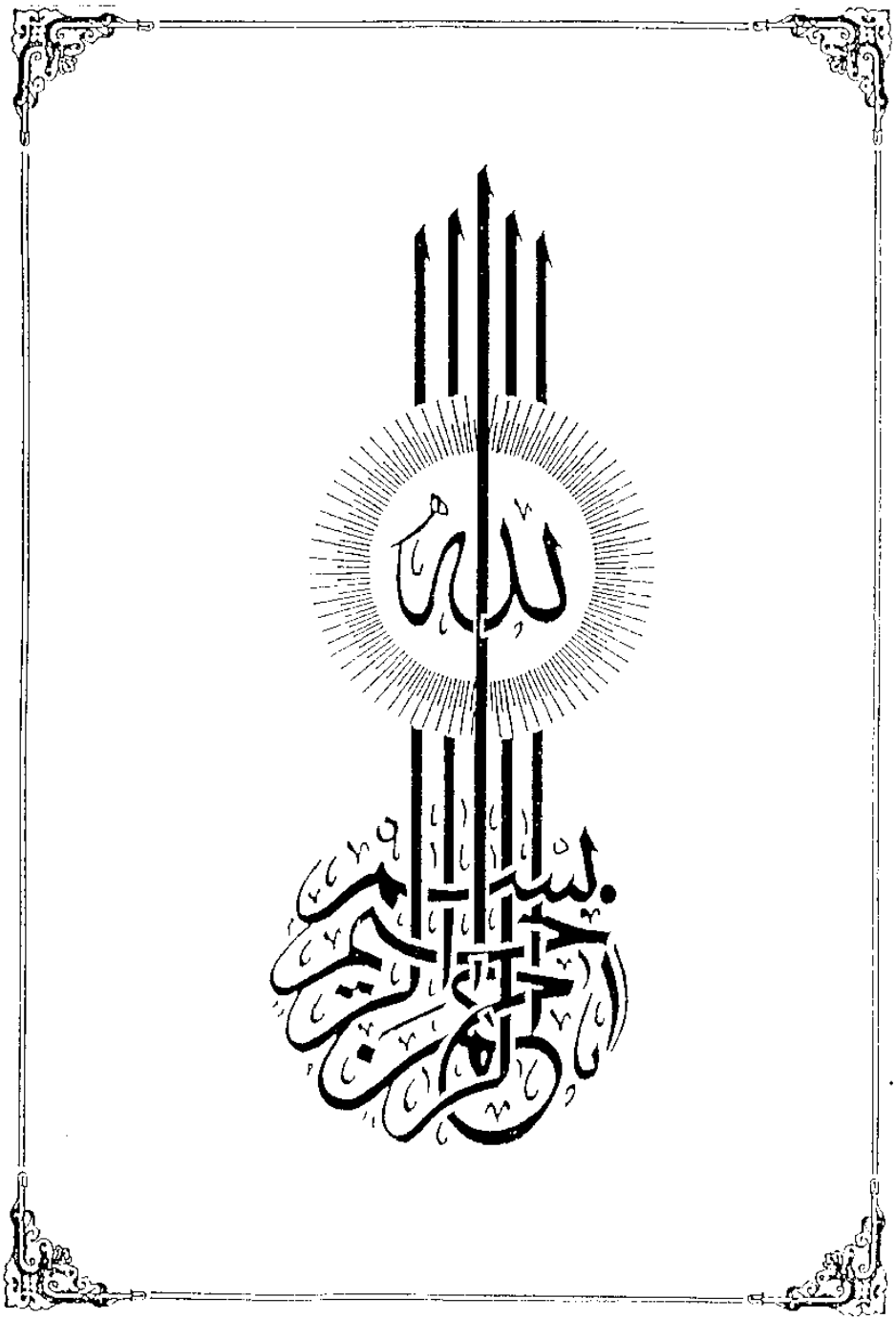

Contents

CHAPTER ONE

NORMAL METABOLISM OF BLOOD LIPIDS

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Composition of Foods:

Since the quantaty and quality of food contribute to the concentration and distribution of blood lipids in various lipoprotein fractions, it is appropriate to discuss briefly the composition of the food we eat.

An average diet contains about 3000 calories, which generally consists of about 40% fats, 48% carbohydrates, and 12% of the total calories are proteins.

The composition of food fat is mostly animal fat, which is mainly saturated fat.

Triglycerides constitute about 98% of food fats, of which 92% to 95% are fatty acids and the remainder is glycerol. The minor fraction, about 2%, of food fats includes cholesterol, phospholipids, diglycerides, monoglycerides, fat soluble vitamins, and other fats.

The individual glycerides molecule in most fats contains both saturated and unsaturated fatty acids.

Several polyunsaturated fatty acids cannot be synthesized in the human body and must be provided in diet. These have been termed "essential fatty acids" (EFA).

The intake of essential fatty acids in human diet is mostly from vegetable sources. (Ganong 1983).

Another principle difference between animal and vegetable fats is the nature of the sterols present. Animal fats' sterol is almost exlusively cholesterol, which is a normal constituent of every animal tissue and a major component of brain, liver, and other tissues, Plant sterols are mainly phytosterols. The phytosterols are important because they compete with cholesterol for uptake by the intestinal mucosal cells. Thus, the more phytosterols is absorbed by the mucosal cells of the gut. (Kaplan, 1984).

Fat digestion, absorption and transport:

Digestive phase:

Most digestion of food fat is carried on in the intestine through the action of intestirol and pancreatic lipases and of bile acids.

Bile salts, produced by the liver and stored in the gall bladdar as bile are both strongly hydrophilic and hydrobolic. Because of their surface active properties, the bile salts emulsify the dietary triglycerides into very small particles that can acted upon by digestive enzymes.

The main path of fat digestion progresses from triglycerides to 1, 2-diglycerides to 2-monoglycerides and fatty acids . Only a small percentage of the fat is hyarolyzed to free fatty acids and glycerol, perhaps after isomerization to the 1-monoglyceride.

In the intestirol lumen the action of a pncreatic lipase on ingested fat results in a complex mixture of triglycerides, diglycerdies, monoglycerides and free fatty acids. (Rommel 1976).

In the intestinal lumen the action of pancratic lipase on ingested fat results in a complex mixture of triglycerides diglycerides, monoglycerides, and free fatty acids. Cholesterol esters are hydrolysed to free cholesterol and free fatty acids, the reaction being catalyzed by the enzyme cholesterol esterase.

For solubilization of the lipids in the intestine, two classes of compounds are essential, namely bile salts lysolecithin. They form a two phase system - an oil phase containing almost all the triglycerides and diglycerides and a water clear micellar solution of momoglycerides, bile salts, lysolecithin, and soaps. (Ganong 1983).

Bile salts combination with the monoglycerdies and fatty acids form a negatively polymalecular aggregates, or "micelles" which are very small in size. Now micelles has access to the intramicrovillus space of the intestinal lumen where penetration into the intestinalmucosal cells can take place. (Rommel 1976).

Absorptive phase:-

The exact mechanism by which micelles are taken into the mucosal cells is not yet clear. (Kaplan 1984).

However, after monoglycerdies and fatty acids enter the endoplasmic reticulum of the mucosal alls, presumably by diffusion, the monoglycerides and fatty acids are reesterified into triglycerides.

The enzyme which is required for fatty acids utilization into triglycerides resynthesis has a pronounced specificity for long chain fatty acids. Thus long chain fatty acids appear in the thoracic duct lymph, and transported as triglycerides in the chylomincrons, whereas short and medium chain fatty acids are transported bound to albumin and transported in the portal circulation. (Rommel 1976).

Transport phase:-

Transport of lipids in plasma is accomplished by the formation of supramolecular complexes called lipoporteins.

The nomenclature of lipoproteins is based on their relative proportions of lipids and protein. These classes do not constitute absolute categories since within each class there is heterogenety with respect to size, and lipid and protein composition. The detailed metabolism of this complexes will be discussed later separately.

Once triglycerides have been resynthesized within the intestinal mucosal cells, they are assembled in the mucosal cell endoplasmic reticulum and the Golgi apparatus

into water soluble macromolecules - chylemicrons and to a small extent, very low density lipoproteins (VLDL), and leave the mucosal cells by pinocytosis.

They first appear in the lympatic vessels of the abdominal region and late in the sytemic circulation. (Rommel 1976).

The blood stream transports chylomicrons and VLDL to all tissues, including adipose tissue. Chylomicrons and VLDL are cleared from the circulation in a matter of minutes and a few hours respectively.

Their triglycerides are hydrolyzed by an enzyme called lipoprotein (or triglyceride) lipase (LPL). This enzyme has been demonstrated in a variety of tissues and its site of action is at the capillary endothelial cell surface (Nelsson 1980).

Under normal conditions, chylomicron catabolism proceeds in two known phases. In the first, triglycerides are hydrolyzed at extrahepatic tissue sites under the influence of a lipoprotein lipase. This process results in a relatively triglyceride poor, cholesterol rich remanant particles. In

the second phase the remant particle is removed by the liver. (Norriset 1975).

Experiments with the perfused organs has shown that the liver does not significantly metabolize native chylomicron or VLDL. (Peter 1983).

Role of Lipoprotien Lipase enzyme:

Lipoprotein lipase is an enzyme (or group of closely related enzymes) generally charcterized by salt inhibition, an alkaline pH optimum, and dependence on apo C II and insulin for optimal catalytic activity. However, difference in chemical and enzymatic characteristics, in immunological behavior, and in hormonal and metabolic regulation raise the question whether LPL from various sources are different proteins? (Nelsson 1980).

Normal blood does not contain appreciable quantities of the enzyme. However, following injection of heparin lipoprotein lipase is released from the tissues into circulation and is accompanied by the clearing of lipemia. LPL is also released from the liver by large quantities of heparin. But this enzyme has properties different from

those of other LPL in being independant on apoprotein C II and insulin for activation, and it does not react readily with chylomicrons. (Brown 1976).

Both phospholipids and apolipoprotein C II are requried as cofactors for LPL activity. Both of this cofactors are present in chylomicron and VLDL (Peter 1983).

The mechanism of hydrolysis of chylomicron trigcerides by LPL is not knwon. The hydrolyzed triglycerides are then progressively degraded into di, and monoglycerides and finally into fatty acids and glycerol. Some of the released free fatty acids return to circulation but the bulk are transported into the tissues where they can be stored, utilized for energy or other fucntions. (Brown 1976).

Reaction with LPL results in the loss of approximately 90% of the triglyceride of chylomicron and in loss of the apo-C polypeptide that return to HDL. The resultant chylomicron remnant will be cleared by the liver, while the VLDL remnant catabolism occur at an extracellur site and results in the formation of LDL, a cholesterol rich particle (Peter 1983).

Role of liver in Lipid metabolism:-

Chylomicron remnant are taken up by the liver and the cholesteryl esters of the remnant are hydrolyzed and the triacylglyceral fatty acids metabolized (Sherrill 1980).

Excess dietary glucose, after repletion of hepatic glycogen stores, is converted to fatty acids. Newly synthesized fatty acids and those derived from diet by direct portol blood transport system are esterified to form triglyceride. This tyriglycerdie is coupled with phospholipid, cholesterol and protiens to form VLDL which are then released into the circulation and transported to adipose tissue.

Hepatic triglyceride synthesis is accelerated when the diet is rich in carbohydrate. This results in VLDL overproduction, which may explain the occasional transient hypertriglyceridemia observed in normal persons when they consume diets particularly rich in simple sugars. (Peter 1983).

Another important source of VLDL triglycerides are the free fatty acids released by adipose tissue. It is not yet established to what extent chylomicrons and VLDL of intestional origin are take up by the liver which could represent another source of hepatic triglyceride. (Salih J.W. 1983).

During fasting, periods of stress, and in certain metabolic conditions, like uncontroled diabetes, free fatty acids derived from adipose tissue are the principal precursor of hepatic VLDL.

Role of adipose tissue in lipids metabolism:-

After a meal, chylomicrons and VLDL fatty acids enter the intracellular free fatty acid pool. Glycerol, on the other hand, is released into the circulation, since adipose tissue lacks glycerokinase, the enzyme necessary to re-esterify glycerol.

Insulin, released in responce to diet, accelerates glucose entery into adipose cells where it is metabolized to glycerophosphate and also to fatty acids, both are the substrates for triglyceride re-synthesis.

High level of insulin accelerates this processes, and after a meal, adipose tissue operates as an effective storage system for alimentary lipids and carbohydrates.

Triglycerides in adipose tissue are constantly subjected to the catabolic action of an intracellular enzyme (different from serum lipoprotein lipase) stimulated by hormones such as catechalamines, thyroxin and glucagon.