A REVIEW ON HYPERLIPIDEMIC

Patel Ravindra*, Devagan Dhanshay and T. Shivkumaran
Nanda College of Pharmacy and Research Center, Erode, T.N.
* Corresponding Author

INTRODUCTION

Atherosclerosis is the major case of morbidity and mortality in the world today, accounting for half of death in world. The origin of atherosclerosis is attributed to diets rich in fats, tobacco, alcohol consumption and lack of physical activity along with genetic factors like increased insulin resistance, decreased β cell function, diabetes mellitus, obesity, and elevated levels of LDL, triglycerides, with reduced HDL Cholesterol (Khan and Butler, 1998).

The events responsible for generation of atheroma include damage of endothelial cell and formation of macrophages engorged foam cells leading to endothelial injury and infiltration of circulating lipoproteins and monocytes, the subsequent chemotaxis and phenotypic changes transform macrophages into foam cells. Atherosclerosis is greatly enhanced in patients with familial Hypercholesterolemia who lack LDL receptors, which are the scavenging receptors present on macrophages and endothelial cells (Ramprasad, 1995).

The next phase involves foam cell migration into the sub endothelial region, which slowly develops there and when stressed can synthesis platelet derived growth factor, which is a powerful chemotactic agent and vasoconstrictor. The other autocrine and paracrine factors present in platelets and atheroma cells include endothelial growth factor interleukin-1, fibroblast growth factor and serotonin, which are mitogenic towards vascular monocytes.

Free radicals damage compounds of all biochemical classes and they have been implicated in causation of several diseases such as liver cirrhosis, atherosclerosis, cancer etc. In in-vivo and health there is a balance between free radical generation and activity of preventive antioxidants like catalase, superoxide dismutase, glutathione peroxidase, ascorbic acid, vitamin E etc. (Jose and Kuttan,1995).

Generation of these free radicals is increased by other risk factor like smoking which may increase free radical stress and thus decreases the bioavailability of nitric oxide (NO). Hypercholesterolemia is shown to diminish production or exaggerated breakdown of NO, which in turn leads to generation of oxygen, derived free radicals (Khan and Butler, 1998). There is a link between the coagulation system and atherosclerosis; raised levels of fibrinogen have been reported in patients with elevated cholesterol and triglycerides levels. Fibrinogen is an acute phase protein associated with risk of deep venous thrombosis. However, increased level of fibrinogen was found to be independent in patients at risk of ischemic heart disease. Abnormalities of fibrinogen metabolism might be liked to lipoprotein abnormalities (lipoprotein (a) and plasminogen). Raised levels of lipoprotein (a) are associated with atherosclerosis, as their structures are common to protein responsible for binding of plasminogen to fibrin to get converted into plasma. Thus by this way lipoprotein (a) might block fibrosis and lead to atherosclerosis. (Thomson and Smith, 1989).

Risk Factors:

I. Hypercholesterolemia:

There is a clear association between cholesterol levels and coronary artery diseases. It is shown that serum cholesterol level above 230 mg/dl increases risk of coronary disease by 11%. In general an increase in every 10 mg/dl cholesterol level increases the risk by about 10%. High level of low density lipoprotein (LDL) is firmly established as risk factor for atherosclerosis, the exact mechanism still being unclear. The oxidative modification hypothesis states that, LDL accumulates in sub endothelial space of arteries and get oxidized to modified LDL which induces vascular cells to produce monocytes, chemo tactic proteins which stimulate further peroxidation of LDL which are negatively charged. Increased negative charge converts the oxidized LDL by scavenger receptors on macrophages form foam cells which further migrate and proliferate to form atherosclerotic plaque (Guyton, 1994; Sharma *et al*., 1992).

HDL is known to play essential role in retrieval of cholesterol by peripheral tissues and by inhibiting oxidation of LDL attributes to the antiatherogenic effect of HDL. Apart from being antiatherogenic in nature HDL is shown to be low in hypertension diabetes mellitus, which increases the risk of atherosclerosis (Krauss and Kesaniemi 1994; Anil *et al*., 1992).

2. Triglycerides:

Role of triglycerides in atherosclerosis is controversial. However several studies have shown that increase serum triglycerides increase the risk to coronary heart diseases. VLDL the carrier of endogenous triglycerides which is encircled by apolipoproteins.Lipoprotein lipase (LPL) present on walls of capillaries is responsible for removal of very low density lipoprotein (VLDL) from circulation. VLDL remnants are likely to be mediated through LDL receptor rather than receptor related protein (RRP).

Elevated levels of triglycerides in blood occur either by over production of VLDL or lipoprotein particle by defective catabolism of triglyceride rich lipoprotein. Hypertriglyceredemia has been shown to be associated with hypercoagulability as high level of triglycerides enhances secretion of plasminogen activator inhibitor and this contributes to decreased fibrinolysis and increased thrombus formation. Increase in triglyceride level may be either due to genetic defects or secondary disorders like diabetes, alcohol, stress and renal failure, which may accelerate atherogenesis (Ramprasad, 1995).

3. Lipoprotein (a) (LP):

Experimental trials have confirmed that high concentration of LP increases risk for coronary heart diseases. LP is similar in structure to LDL, which might bind and prevent fibrinolysis, as it is homologues to plasminogen (Berkel 1994). LP is now recognized as risk factor for premature atherogenesis. As LP after oxidation stick to macrophages and promote their transformation into foam cells. Hypertension, chronic infection, smoking, obesity and diabetes (Guyton, 1994; Saxena and Goldberg, 1994; Lawn, 1992) aggravate this oxidation of LP.

4. Blood Pressure:

Hypertension can produce mechanical stimuli and can stimulate synthesis of mitogenic agents, which promote the formation of foam cell and aggregation of platelets leading to atherogenic plaque, hypertension when prolonged causes injury to endothelium and promotes atherogenesis through cytokinin release.

5. Free Radicals:

Oxygen derived free radicals like superoxide, thyl; trichloromethyl and nitric oxide are examples of free radicals. These free radicals trigger oxidation of lipids, DNA, proteins and distract the cells. Any injury to endothelium promotes monocyte recruitment and its conversion to foam cells with enhanced platelet aggregation at the site of injury resulting in accelerated atheroma formation (Ardlie and Han, 1973). Oxidative stress mediates injury to endothelium and also oxidizes LDL which might contribute to platelet adhesion and vasospasm which are involved in pathogenesis of atherosclerosis. (Halliwell *et al*., 1992; Epstein, 1992).

6. Cigarette Smoking:

The possible mechanisms which associates smoking and atherosclerosis is by release of adrenaline stimulated by nicotine leading to increase free fatty acids which subsequently lead to increased synthesis and release of cholesterol and thus contribute to atherosclerosis. Besides this, cigarette smoking alters coagulation system and produce free radicals like NO, which attribute to accelerated atheroma formation (Khan and Butler, 1998).

7. Coagulation System:

Atherosclerosis results from thrombosis, which has been established in experimental models. Injury to endothelial arterial wall increases platelet interaction with sub endothelium forming small platelet thrombi, which migrates from intima to subintima and proliferates leading to atheroma. Tissue factor (TF) is predominant initiator of coagulation. Expression of TF is induced by oxidized LDL and plasminogen activator inhibitor leading to myocardial thrombosis and fibrous plaque rupture resulting in hemorrhage and hypercoagulable stage, which promotes arterial thrombosis. (Miller, 1995).

Factor VII is activated by TF which forms factor VII activated tissue factor complex, which in turn initiates activation of factor IX and factor X leading to blood coagulation. Further increase in factor VII as in hypertriglyceredemia has been established in hypercholesterolemia rabbits which lipolysis triglycerides rich lipoproteins. (Diaz *et al*., 1997).

In-vitro studies have shown VLDL induces plasminogen activator inhibitor secretion and reduces fibrinolytic capacity. In addition proinsulin and insulin like growth factor

impair endogenous fibrinolysis by stimulating secretion of plasminogen activator inhibitor. (Thomson and Smith, 1989).

8. *Platelet aggregation*:

Human platelets do not replicate and thus have relatively short half-life. Yet they are reported to participate in atheroma formation. Though platelets are non-sticky they turn sticky with slight stimulation by adrenaline, ADP, collagen and laminin. After becoming sticky, platelets change their shape and adhere to collagen and thus to sub endothelium. Aggregated platelets secrete contents into surrounding medium leading to aggregation of adjacent platelets, which is irreversible.

Platelet derive growth factor (PDGF) is a stimulator of smooth muscle cell migration by activation of 12 HETE (12-α, hydroxy- 5,8,10, 14 eicosatetraenoic acid) which confirms atheroma formation. Heparitinase in platelets inactivate heparin and heparin like proteoglycans, which promotes smooth muscle cell proliferation and coagulation. Besides these mechanism platelets secrete thromboxin A_2 a potent vasoconstrictor and platelet aggregating agent. (Prentice, 1999; Lefkovits *et al*., 1998)

ADP is contained in the dense granules of platelets and is released when platelets are stimulated by agonists such as thrombin and collagen. Subsequently, ADP activates glycoprotein (Gp) IIb/IIIa receptors, resulting in platelet aggregation. ADP induced platelet aggregation is a major factor in the promotion and extension of thrombosis. The central of ADP induced activation is emphasized by the effectiveness of antiplatelet drugs that act at this site.

9. Other Factors:

1. Chronic heart disease
2. Diabetes mellitus,
3. Impaired carbohydrate catabolism,
4. Lack of physical exercise.

From the above review it is clear that the following factors promote atherosclerosis

1) Hyperlipidaemia
2) Cigarette Smoking
3) Diabetes mellitus
4) Free radicals
5) Coagulation System

LIPOPROTEIN PARTICLES

Following are the major lipoprotein particals:

Chylomicron VLDL,LDL,HDL

Chylomicrons

Chylomicrons are assembled in the intestinal mucosa as a means to transport dietary cholesterol and triacylglycerols to the rest of the body. Chylomicrons are, therefore, the molecules formed to mobilize dietary (exogenous) lipids. The predominant lipids of chylomicrons are triacylglycerols. The apolipoproteins that predominate before the chylomicrons enter the circulation include apoB-48 and apoA-I, -A-II and IV. ApoB-48 combines only with chylomicrons.

Chylomicrons leave the intestine via the lymphatic system and enter the circulation at the left subclavian vein. In the bloodstream, chylomicrons acquire apoC-II and apoE from plasma HDLs. In the capillaries of adipose tissue and muscle, the fatty acids of chylomicrons are removed from the triacylglycerols by the action of lipoprotein lipase (LPL), which is found on the surface of the endothelial cells of the capillaries. The apoC-II in the chylomicrons activates LPL in the presence of phospholipid. The free fatty acids are then absorbed by the tissues and the glycerol backbone of the triacylglycerols is returned, via the blood, to the liver and kidneys. Glycerol is converted to the glycolytic intermediate dihydroxyacetone phosphate (DHAP). During the removal of fatty acids, a substantial portion of phospholipid, apoA and apoC is transferred to HDLs. The loss of apoC-II prevents LPL from further degrading the chylomicron remnants.

Chylomicron remnants containing primarily cholesterol, apoE and apoB-48--- are then delivered to, and taken up by, the liver through interaction with the chylomicron remnant receptor. The recognition of chylomicron remnants by the hepatic remnant receptor requires apoE. Chylomicrons function to deliver dietary triacylglycerols to adipose tissue and muscle. And dietary cholesterol to the liver. (Farese *et al*., 2000)

Very Low Density Lipoproteins (VLDLs)

The dietary intake of both fat and carbohydrate, in excess of the needs of the body, leads to their conversion into triacylglycerols in the liver. These triacylglycerols are packaged into VLDLs and released into the circulation for delivery to the various tissues (primarily muscle and adipose tissue) for storage or production of energy through oxidation. (Gregg and Wetterau, 1994)

VLDLs are, therefore, the molecules formed to transport endogenously derived triacylglycerols to extra-hepatic tissues. In addition to triacylglycerols, VLDLs contain some cholesterol and cholesteryl esters and the apoproteins, apoB-100, apoC-I, apoC-II, apoC-III and apoE. Like nascent chylomicrons, newly released VLDLs acquire apoCs and apoE from circulating HDLs. The fatty acid portion of VLDLs is released to adipose tissue and muscle in the same way as for chylomicrons, through the action of lipoprotein lipase. (Mahley and Ji, 1999)

The action of lipoprotein lipase coupled to a loss of certain apoproteins (the apoCs) converts VLDLs to intermediate density lipoproteins (IDLs), also termed VLDL remnants. The apoCs are transferred to HDLs. The predominant remaining proteins are apoB-100 and apoE. Further loss of triacylglycerols converts IDL to LDL.

Intermediate Density Lipoproteins (IDLs)

IDLs are formed as triacylglycerols are removed from VLDLs. The fate of IDLs is either conversion to LDLs or direct uptake by the liver. Conversion of IDLs to LDLs occurs as more triacylglycerols are removed. The liver takes up IDLs after they have interacted with the LDL receptor to form a complex, which is endocytosed by the cell. For LDL receptors in the liver to recognize IDLs requires the presence of both apoB-100 and apoE (the LDL receptor is also called the apoB-100/apoE receptor). The importance of apoE in cholesterol uptake by LDL receptors has been demonstrated in transgenic mice lacking functional apoE genes. These mice develop severe atherosclerotic lesions at 10 week of age.

Low Density Lipoproteins (LDLs)

The cellular requirement for cholesterol as a membrane component is satisfied in one of two ways: either it is synthesized *de novo* within the cell, or it is supplied from extra-cellular sources, namely, chylomicrons and LDLs. As indicated above, the dietary cholesterol that goes into chylomicrons is supplied to the liver by the interaction of chylomicron remnants with the remnant receptor. In addition, cholesterol synthesized by the liver can be transported to extra-hepatic tissues if packaged in VLDLs. In the circulation VLDLs are converted to LDLs through the action of lipoprotein lipase. (Innerarity *et al,* 1990; Pullinger *et al,*, 1995)

LDLs are the primary plasma carriers of cholesterol for delivery to all tissues. The exclusive apolipoprotein of LDLs is apoB-100. LDLs are taken up by cells via LDL receptor-mediated endocytosis, as described above for IDL uptake. The uptake of LDLs occurs predominantly in liver (75%), adrenals and adipose tissue. As with IDLs, the

interaction of LDLs with LDL receptors requires the presence of apoB-100. The endocytosed membrane vesicles (endosomes) fuse with lysosomes, in which the apoproteins are degraded and the cholesterol esters are hydrolyzed to yield free cholesterol. The cholesterol is then incorporated into the plasma membranes as necessary. Excess intracellular cholesterol is re-esterified by acyl-CoA-cholesterol acyltransferase (ACAT), for intracellular storage. The activity of ACAT is enhanced by the presence of intracellular cholesterol. Insulin and tri-iodothyronine (T3) increase the binding of LDLs to liver cells, whereas glucocorticoids (e.g., dexamethasone) have the opposite effect. The precise mechanism for these effects is unclear but may be mediated through the regulation of apoB degradation. (Nakata *et al,* 1999)

The effects of insulin and T3 on hepatic LDL binding may explain the hypercholesterolemia and increased risk of atherosclerosis that have been shown to be associated with uncontrolled diabetes or hypothyroidism. An abnormal form of LDL, identified as lipoprotein-X (Lp-X), predominates in the circulation of patients suffering from lecithin-cholesterol acyl transferase. In both cases there is an elevation in the level of circulating free cholesterol and phospholipids. (Dhaliwal and Steinbrecher, 1999)

High Density Lipoproteins, HDLs

HDLs are synthesized *de novo* in the liver and small intestine, as primarily protein-rich disc-shaped particles. These newly formed HDLs are nearly devoid of any cholesterol and cholesteryl esters. The primary apoproteins of HDLs are apoA-I, apoC-I, apoC-II and apoE. In fact, a major function of HDLs is to act as circulating stores of apoC-I, apoC-II and apoE. HDLs are converted into spherical lipoprotein particles through the accumulation of cholesteryl esters. This accumulation converts nascent HDLs to HDL_2 and HDL_3. Any free cholesterol present in chylomicron remnants and VLDL remnants (IDLs) can be esterified through the action of the HDL-associated enzyme, lecithin cholesterol acyltransferase, LCAT. LCAT is synthesized in the liver and so named because it transfers a fatty acid from the C-2 position of lecithin to the C-3-OH of cholesterol, generating a cholesteryl ester and lysolecithin. (Maciejko *et al,* 1983)

The activity of LCAT requires interaction with apoA-I, which is found on the surface of HDLs.Cholesterol-rich HDLs return to the liver, where they are endocytosed. Hepatic uptake of HDLs, or reverse cholesterol transport, may be mediated through an HDL-specific apoA-I receptor or through lipid-lipid interactions. Macrophages also take up HDLs through apoA-I receptor interaction. HDLs can then acquire cholesterol and apoE from the macrophages; cholesterol-enriched HDLs are then secreted from the

macrophages. The added apoE in these HDLs leads to an increase in their uptake and catabolism by the liver. (Williams *et al,* 1999)

HDLs also acquire cholesterol by extracting it from cell surface membranes. This process has the effect of lowering the level of intracellular cholesterol, since the cholesterol stored within cells as cholesteryl esters will be mobilized to replace the cholesterol removed from the plasma membrane.(Krieger and Kozarsky,1999)

The cholesterol esters of HDLs can also be transferred to VLDLs and LDLs through the action of the HDL-associated enzyme, cholesterol ester transfer protein (CETP). This has the added effect of allowing the excess cellular cholesterol to be returned to the liver through the LDL-receptor pathway as well as the HDL-receptor pathway.

MECHANISM OF LIPID TRANSPORT

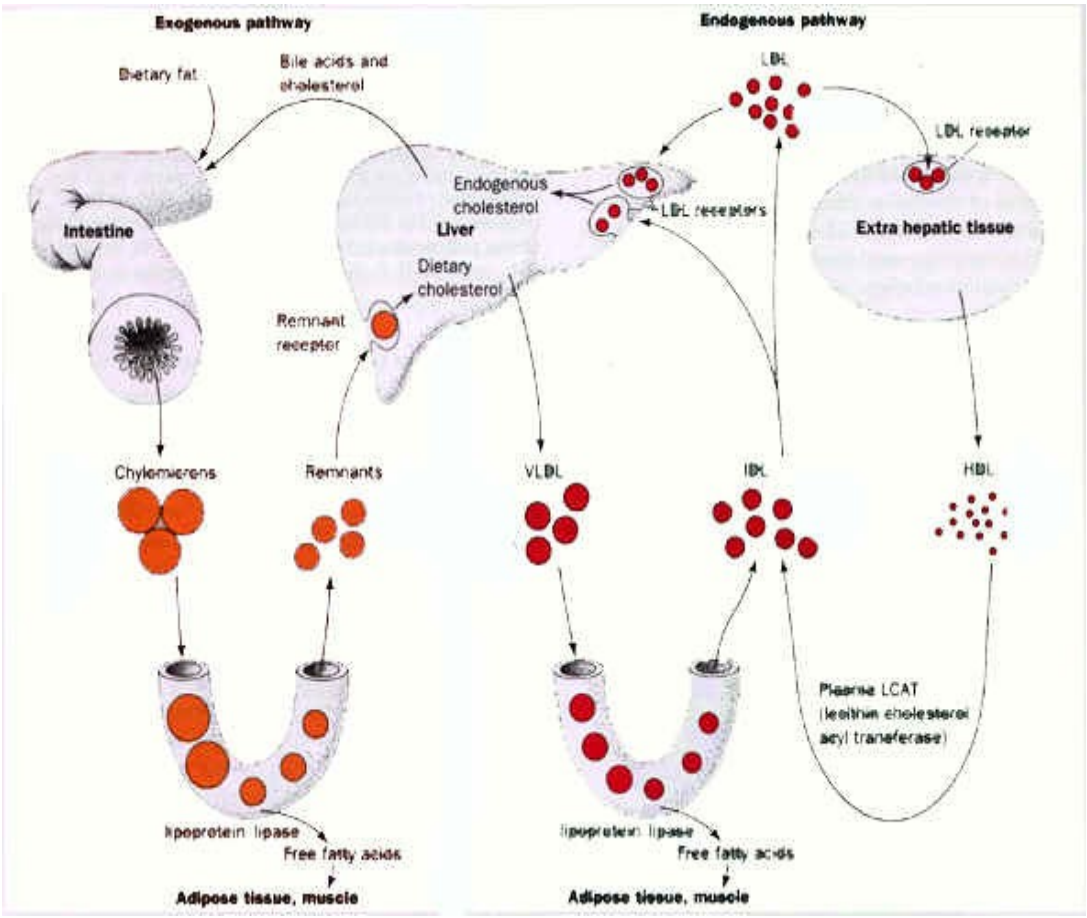


Fig: 1 Mechanism of Lipid Transport (Lipids Online, 2007)

LIPOPROTEIN LIPASE (LPL):

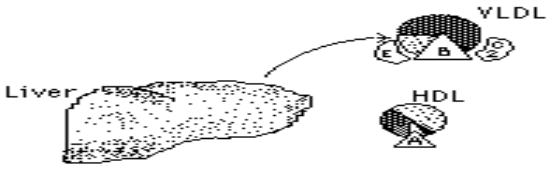


Fig: 2 Mechanism of action of Lipoprotein Lipase (Lipids Online, 2007)

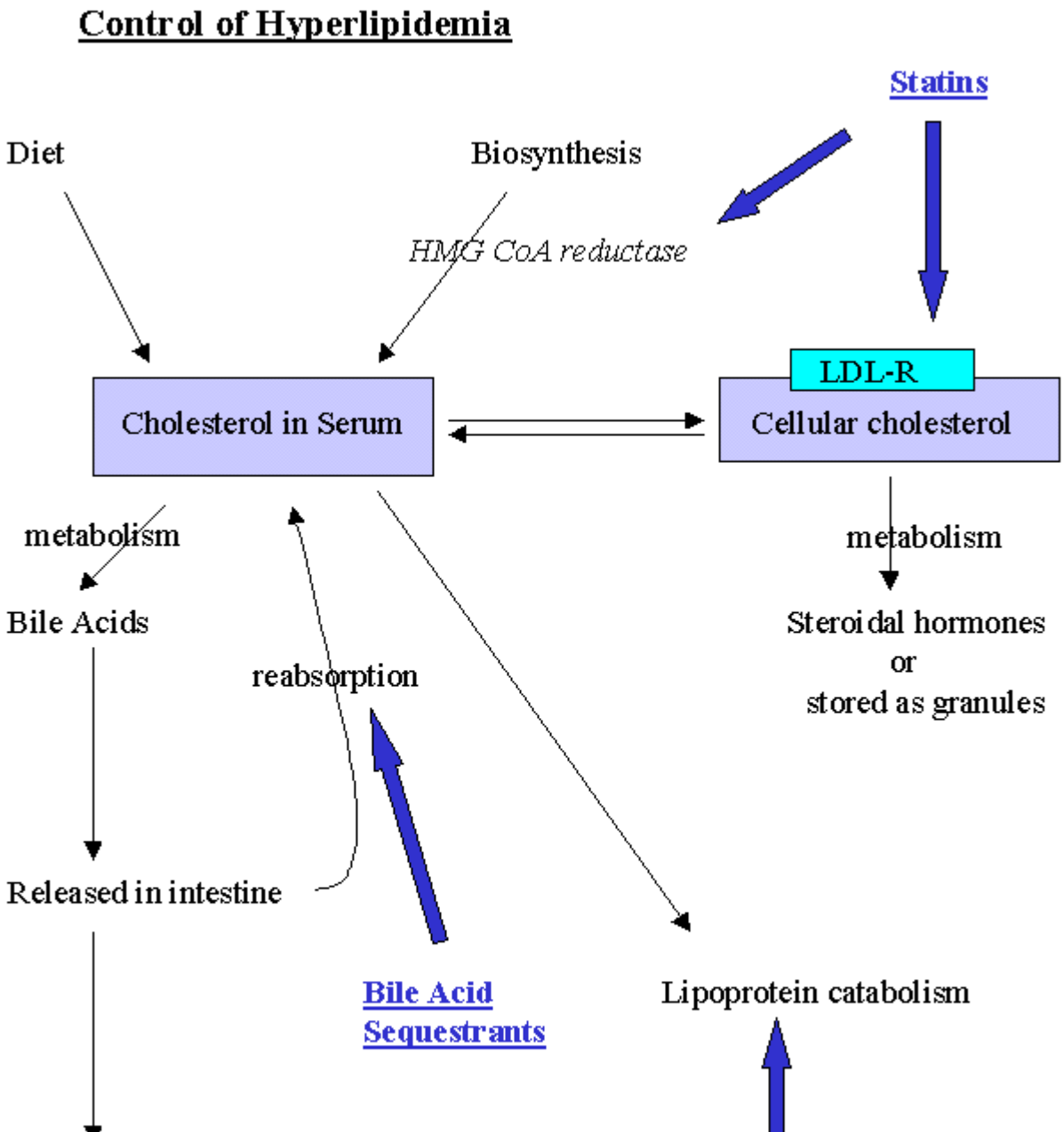
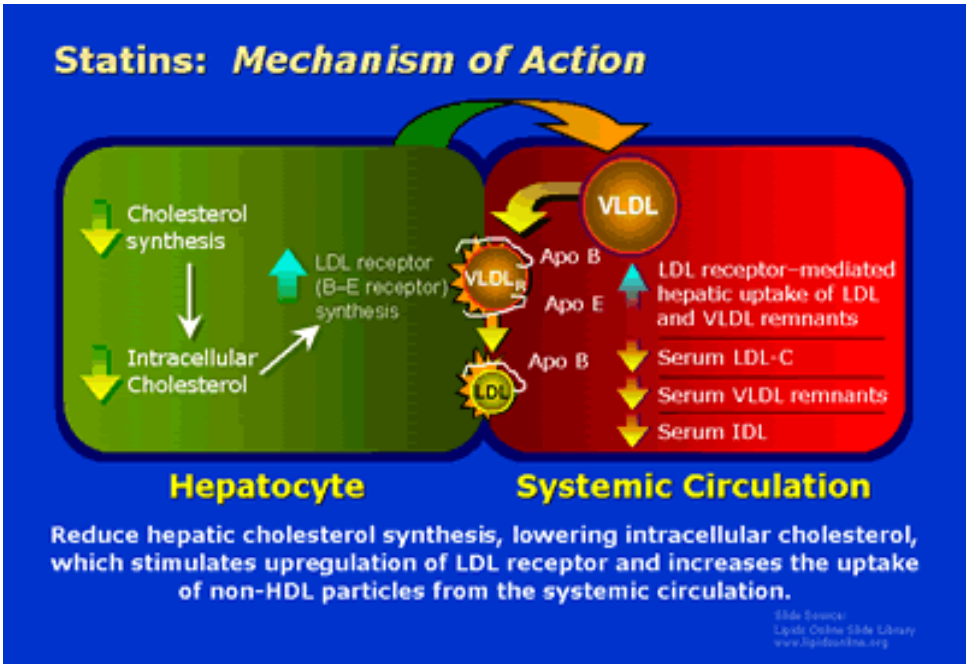

Control of Hyperlipidemia
Statins
Diet
Biosynthesis
HMG CoA reductase
LDL-R
Cholesterol in Serum
Cellular cholesterol
metabolism
metabolism
Bile Acids
Steroidal hormones
or
stored as granules
reabsorption
Released in intestine
Bile Acid
Sequestrants
Lipoprotein catabolism

Fig: 3 Control of Hyperlipidemia (Lipids Online, 2007)

ANTIHYPERLIPIDEMIC DRUGS

Statins: eg. Atorvastatin ,Simvastatin, Rosuvastatin etc.



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