REVIEW OF LITERATURE
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Recent studies suggest that low density lipoprotein (LDL) are main culprit of otherosclerosis. LDL are rapidly taken up by arterial smooth muscles and arterial endothelial cells [Rose et. al 1976]. Serum low density lipoprotein (LDL) are main carrier of cholesterol and apoproteins both which have been found in Atherosclerotic Patch [Hoff et. al 1973].

Plasma lipid and lipoprotein concentration in man and woman vary with age, total cholesterol value are higher in man as compared to woman between age 20-55 year. Values of VLDL are similar in both sex at 20-59 years, Values of HDL are higher in woman then man through out the age range.

High density lipoprotein HDL is protective in nature, major role of HDL is centripetal transport of cholesterol from peripheral tissue to liver (clornset, 1963) and indirectly it facilitates transport of triglycerids.

Woman taking sex harmones have higher total cholesterol then nontakers between age 20-50 years. In chronic renal diseases the serum cholesterol and serum triglyceride tend to be elevated. Elevation is inversely related with serum albumin level more than 40% of young patients of documented coronary artery disease are normal cholesterolemic (Gregory et. al. 1983).

Chiba et al (1984) observed variability of serum high density lipoprotein cholesterol concentration in healthy subjects in 3 years term
and find that mean HDL and serum total cholesterol values varied to some extent year by year when effect of age and menopause was eliminated they concluded that non mormolipidemic people had wider individual variation both in high density Lipoprotein (HDL) and triglyceride.

Natelson and others: Concentration of Serum cholesterol can vary during day both serum cholesterol (STC) & High density lipoprotein (HDL) cholesterol concentration to be in evening and lowest in early hours of morning shows diurnal variation.

Heggsted DM et al (1987). observed a large difference in serum cholesterol level of same subject by unknown reason. In a single sample from a man with mean serum cholesterol level 220 mg/dl can be expected to fall between 200 and 220 mg/dl - A RANGE FROM NO RISK TO HIGH RISK. Many individual may show greater variation then this [Blank et al 1986] variety of methods are available to estimate serum cholesterol but may not yield same absolute values.

In the studies of our department [Arora & Sharma 1984]. The effect of high cholesterol fat diet after single dose was studied in healthy subjects & subjects of ischemic heart disease, diabetes mellitus and chronic renal disease. Post prandial changes were observed in serum total cholesterol, low density lipoprotein and serum triglycerides.

[Rose and Glomet 1976] : It has been found that in atherosclerotic lesion there is smooth muscle proliferation along with large amount of connective tissue matrix and intracellular and extracellular lipid.
Each cell responds to different atherosclerosis lies in the intima of vessels
in form of fatty streaks of Plaque [Gill 1977].

In a study carried out in our department Arora & Umashanker
(1993) majority of healthy effects of single high cholesterol fat diet was
observed on healthy individuals and patients of diabetic mellitis
Hypertension and ischemic heart disease. Majority of healthy population
showed a fall in serum total cholesterol and low density lipoprotein(LDL) at
one hour & patients of diabetes mellitus, Hypertension & ischemic heart
disease minority of healthy subjects revealed rise in serum total cholesterol
(STC) and low density lipoprotien (LDL) in one hour.

In earlier report (BRAHN 1940) observed a 20% rise in mean
cholesterol level after a test dose of cholesterol.

There are atleast three independent predictors of risk for
individuals. There are Plasma cholesterol concentration, [RAM 1986,
INKELES and EISENBERG, 1981] cigarette smoking [WISSLER, 1976],
and elevated blood pressure [OBERMAN, HARLEN et al 1969]

Recently some workers have shown the existence of cell
surface receptors for low density lipoprotein [GOELSTEIN et. al 1974]
which explains the mechanism of plasma cholesterol control.

MOGADM. M, AHMEDS W, MENSHEH (1990) measured
fasting total serum cholesterol & lipoproteins variation of more than ± 20%
in serum level of total cholesterol, low density lipoprotein cholesterol and
high density lipoprotein cholesterol were seen in 75%, 90% and 65% of
subjects respectively, on observation , 40% of subjects moved in or out of
one risk category and in 10% two categories from desirable to high risk or vice versa. These data demonstrate that random testing may fail to detect wide fluctuation in level of serum lipoprotein & therefore result in erroneous risk assignment or therapeutic intervention [ARCH INTERN MED 1990, 150 (8) 1583-5] various hypothesis have been proposed to explain atherosclerosis. Dietary fat cholesterol and raised plasma cholesterol are one of the major risk factors for atherosclerosis.

LAREN (1966) observed that reduction in dietary cholesterol however has no change in subjects above 60 year of age, when Polyunsaturated fat have been substituted for saturated fats in diet it will lower serum cholesterol but not serum triglyceride [AHRENS et al ; 1957; KINSELL et al 1952, GRUNDY, 1975]

Serum cholesterol was higher during the first 9-12 months of life in breast fat babies because breast milk is rich of cholesterol. In subsequent life there was little differences [ FRIEDMAN AND GOLDBERG 1976, HUTTMAN et al 1983].

Previous study (Arora et al, 1987) showed that dietary cholesterol and fat have definite relation to serum lipid the study was done to evaluate the changes in serum lipoprotein after ingestion of high cholesterol fat diet in selected number of subjects. It showed that the basal values of various lipoprotiens were normal at their age and rise occurred in all lipoprotein after ingestion of high cholesterol fat diet.

Atherosclerosis is a diseases of large and medium sized muscular arteries and has a basic lesion : Atheroma of fibrofatty plaque consisting of raised focal plaque within the intima having a layer of lipid mainly cholesterol usually complexed to proteins and cholesterol esters
and a covering fibrous cap (Robbins and Cotran, 1984). The possible mechanism by which HDL cholesterol decreases atherosclerosis includes:

1. Reversal of cholesterol transport from the peripheral cells to the liver for removal from the body (Miller and Miller, 1975).

2. Inhibition of LDL cholesterol uptake by cells at the LDL receptor sites.

**FAT TOLERANCE TEST AND ITS IMPLICATIONS**

The concept of fat/cholesterol tolerance test is not entirely new. In 1907, Neuman after giving a fat load studied the quantitative lipid changes in from the of chylomicron count after a fat load.

Introduction of isotopes, revoluiosned the study of lipid metabolism. Brekowitz (1963). Pointed out that radioactive fat tolerance is a better index for determining the functional state of lipid metabolism.

If atherosclerosis is a post prandial phenomenon then premature CAD must be common in hyperchylomicronemic states. However, in familial lipoprotein lipase deficiency enormous quantities of chylomicrons accumulate in plasma, but accelerated atherosclerosis has not been reported (Fredrickson et al, 1970).

HDL levels are lower in obese individual than in non obese controls (Wilson et al, 1972 : Carlson et al.1975 and Glueck et al). During the course of weight loss, an increase in HDL cholesterol concentration has been reported to occur in association with reduction in VLDL and total

Serum cholesterol levels have been reported to be higher in postmenopausal compared with premenopausal women of same group in several population in the united state and North Europe (Halberg et al, 1957; hjortland et al, 1976; Lindquist et al, 1980). A rise in serum cholesterol with menopause has also been reported in Japanese women (Shibata et al. 1963).

The women using oral contraceptive that are higher in estrogen and low in progestin contest had significant high concentration of HDL cholesterol than those not using the hormones (Glose et al, 1974; Hironen et al, 1981; and Larsson Cohn et al. 1979).

The basic defect in reduced number of LDL receptors. In normal person about 45 poercent of the plasma LDL pool is removed from the plasma daily by the receptors where in familial hypercholesterolemia heterozygotes this value is 25-30 percent and in homozygotes it is about 15 Percent. The receptor deficiency results in accumulation of LDL into the plasma leading to raised level and premature atherosclarosis.

The Fremingham’s study (1976) showed that in men and women 35-44 years of age, serum cholesterol levels 265 mg/dl or more have five times higher risk of IHD than are levels 220 mg/dl or less. The most striking association with atherosclerosis (AS) and IHD is with elevated levels of LDL (Weiss et al, 1972). But Hyperlipidemia with increased
concentraduon of VLDL also appears to increase the risk. In contrast serum levels of HDL are inversely related to risk (Heirs et al 1980).

CONTROL OF PLASMA CHOLESTEROL LEVEL BY LDL RECEPTORS

A decade of intense investigation has established a central role for lipoprotein receptors in regulating plasma cholesterol. Operationally, the IDL/LDL receptor system can be considered the primary transport mechanism for endogenous cholesterol. LDL are generated in the plasma by the degradation of intermediate density lipoprotein (IDL). Generated LDL is removed relatively slowly from plasma by binding to LDL receptors in the liver and extra hepatic tissues (Kita et al, 1982). However, the precise distribution of these receptors in man is unknown.

REGULATION OF HEPATIC LDL RECEPTORS

Hepatic LDL receptors are suppressed whenever the liver content of cholesterol increases or its demand for cholesterol is reduced. Thus receptor suppression occurs when a high cholesterol diet is consumed (Hui et al, 1981) or when bile acids are infused (Angelin et al, 1983). Conversely, LDL receptors increase when hepatic cholesterol synthesis is blocked by drugs compactin or mevinolin (Goldstein et al, 1982 and Bilheimer et al, 1983).

LIPID METABOLISM

EXOGENOUS PATHWAY

The chylomicrons, large triglycerides rich particles are produced in the intestine from dietary fat. Hence they are normally not
present in plasma after fast of 12-14 hours. They are catabolized by lipoproteins lipase (LPL) and hepatic lipase (HL) to form chylomicrons remnants, triglycerides form free fatty acids (FFA). Apo E facilitates the uptake of these remnants while Apo C-III inhibits it.

**ENDOGENOUS PATHWAY**

VLDL synthesis occurs in liver and is increased in obese persons and is inhibited by the uptake of chylomicrons remnants. VLDL, triglycerides and phospholipids are hydrolyzed by lipoprotein lipase and hepatic lipases. During this apo E and apo C of VLDL is transferred to HDL while apo B-100 remains within. Thus the end product of VLDL catabolism are LDLS.

LDLs are major cholesterol carrying lipoproteins in normal plasma in humans and most of it comes from VLDL catabolism while some are synthesized directly (in subjects of homozygous familial hypercholesterolemia). The major protein of LDL is apo B-100 is catabolized in various cell types by receptor dependent as well as receptor independent mechanism. LDL when degraded in cell results of from free cholesterol which in turn inhibits the enzyme (3 hydroxy, 3 methylglutaryl coenzyme A reductase) producing it.

Direct HDL production occurs in liver and intestines and also derived from chylomicrons and VLDL catabolism. Moreover, HDL serves as acceptor of lipid especially free cholesterol. Apo I and II are major protein in HDL. Hepatic lipases metabolise HDL phospholipids and triglycerides and liver and kidney are major sites for catabolism.
CHYLOMICRONS

It is the largest of the lipoproteins originating from the gut mainly composed of triglyceride and transport dietary triglyceride and cholesterol from gut to site of metabolism or storage. In post prandial state it is detacted by "creaming in the cold".

Dietary fat is broken down to free fatty acids and monoglycerides in intestine which then enterintestinal villi in jejunum reconstituting into triglyceride. In the cells of jejunum cholesterol is esterified to cholesteryl ester (Oleate). The triglyceides are then complexed with Apo B-48, apo Al & II A-IV within intestinal wall. The chylomicrons enter systemic circulation via lymphatics, Apo E and apo C proteins are added in lymph or blood. Chylomicrons are rapidly cleaned from blood by lipoprotein lipases and results in formation of partially degraded chylomicrons particles called remanants which are taken up by liver.

Chylomicrons in fasting state is abnormal and has been postulated that prolonged clearance of dietary remnant particles could be damaging to vascular endothelium and may predispose to atherosclerosis.

VLDL

It is endogenously produced lipoprotein (in liver) and contains apo B-100. It’s synthesis is increased in obesity, alcohol use and diabetes, nephrotic syndrome and hypothyroidism. Its function is to transport cholesterol and endogenously produced triglyceride. Clefsky et al (1976) noted biphasic plasma triglyceride curve. An initial peak occurred 1-3 hours after feeding was accounted by increase in chylomicrons levels in more than 98% and second peak after 4-7 hours accounted for rise in VLDL level in 82%.
IDL

It is formed from metabolism of VLDL of which roughly half is metabolized in mass and remainder half in converted to LDL. The elevation of IDL is also thought to predispose for atherosclerosis.

LDL

It is produced from VLDL in plasma, and LDL supplied cholesterol to extrahepatic parenchymal cells, as adrenal cortical cells, lymphocytes, muscle cells etc. Thus Goldstein (1977) hypothesized the concept of LDL receptors and has been confirmed by many laboratories. These receptors are over cell surfaces to which LDL binds and by endocytosis, it is digested by lysosomes interact with cholesterol for membrane synthesis and precursors for steroid hormone synthesis. Liver uses LDL for synthesis of bile acids and free cholesterol secreted in bile. Diet high in fat and cholesterol causes elevation of LDL but varies in man.

Age related difference in rise of LDL was demonstrated by Arora and Gupta G (1987). They found out that rise of STC after feeding high fat breakfast for one week was much more pronounced in young volunteers (20-30 years) with major portion of rise contributed by HDL. Contrary in other persons the rise of STC was less marked and LDL mainly contributes to it.

HDL

It is produced in gut, by liver and also by peripheral catabolism of chylomicrons and VLDL. They are reservoirs for apolipoproteins. Some investigators have proposed that HDL facilitates cholesterol removal from
cells particularly of reticuloendothelial system (Schnitz and Robenek et al, 1985). It is thus termed reverse endocytosis.

HDL is subdivided into several fractions in which HDL$_2$ and HDL$_3$ are important and best studied. HDL$_2$ are large and more lipid rich than HDL$_3$. Concentration of HDL$_2$ is higher in woman than in man and are increased by oestrogen or physical activity (Exercise). Alcohol also increases both HDL$_2$ and HDL$_3$. Factors in which HDL lowers are hypertrigly ceridemia, cigarette smoking. Exogenous androgen administration lowers HDL levels in man (Furman et al, 1967). A drop in HDL level is seen in males at around the time of puberty (Beagtehole et al, 1980) and has been related to degree of sexual matuation (Frerich et al , 1978 and Morrison et al, 1979). Transient increase of HDL2 has been reported at time of ovulation (Barclay et al, 1965). No changes in HDL is found during pregnancy.

HDL level changes with age. In males levels are stable uptill puberty after which there is decline followed by stable levels in adulthood until 55-60 years where there is increase and then a plateau in older age group. In females there is a small linear increase in levels from childhood to about 60 years.Reduction in obesity by mild exercise programme resulted in no increase in HDL cholesterol while drop in HDL levels are found in those with caloric restriction in absence of exercise.

**Effect of Dietary cholesterol on lipid metabolism**

Additions of dietary cholesterol has been known to increase plasma cholesterol levels and induce arteriosclerosis in experimental
animals. Subsequently cholesterol rich diets have regularly caused hypercholesterolemia, atherosclerosis and even myocardial infarction in a large number of experimental animals including primates (Taylor et al, 1950; Armstrong et al, 1967; 1970). A decisive effect of cholesterol in the diet of man upon the serum lipid levels was clearly demonstrated in series of metabolic ward experiments being carried out in normal volunteers (Beveridge et al, 1960; Conner et al, 1961; 1964).

Absorbed cholesterol is transported from the gut in chylomicrons, largely as esterified cholesterol and reaches a peak concentration in plasma 48 hours after meal. Chylomicrons are converted into chylomicron remnants after the action of lipoprotein lipase in peripheral tissues. The cholesterol of remnants contributes its mass to the total body pools of cholesterol (Bhattacharya et al, 1976).

The increased cholesterol uptake may :-

1. Inhibit new cholesterol synthesis.

2. Increase esterol excretion in the bile as bile acids or as cholesterol itself.

3. Increase excretion of cholesterol from the liver as nearly synthesized lipoproteins primary VLDL.

**Effect of carbohydrates of plasma lipid levels**

Carbohydrates induction occur when 70-80% of calories are supplied by carbohydrate. In carbohydrate induction plasma triglyceride level start to increase transiently plasma triglyceride level start to increase
transiently (Ahrens et al, 1961). Individuals on high carbohydrate diet have insignificant rise in triglyceride level and low incidence of atherosclerosis (Conner and Conner 1972)

**Effect of calories on plasma lipid level**

The consumption of high calories (more than basal requirement) is associated with obesity in which cholesterol synthesis is increased (Dennion and Grundy, 1975). Carlson et al (1975) and Garrison et al (1980) reported the elevated levels of VLDL, LDL and reduction in HDL is associated with obesity. These consequences are due to increased synthesis of VLDL, triglyceride and decreased clearance of VLDL, triglyceride and decreased clearance of VLDL from after high calories supplementation.

**Effects of Dietary fat on lipid metabolism**

The amount and kind of fat in diet has a well documented effect upon plasma lipid concentration (Ahrens et al, 1957 ; keys et al, 1957). A fatty meal will result in the productions of large number of chylomicrons. The effects of dietary fat upon plasma concentration depends on the type of fat consumed. Long chain saturated fatty acids are not essential nutrients and may be synthesized in the body from acetate. Dietary saturated fatty acids increases the LDL concentration (Ahrens et al, 1957 ; and Keys et al, 1957). All the animal fats except fish are highly saturated.

These are no essential fatty acids and have no effect on plasma lipid. They are readily synthesized in body. Polyunsaturated fatty
acid (prostaglandin precursors) are important constituents of cell membrane. They are rich in vegetables oils, fish and shellfish. These polyunsaturated fatty acids serve as substrate for the formation of different prostaglandin and concentrated in nervous tissue retina, spermatozoa, adrenal glands and many other organs. They depress plasma cholesterol and LDL concentration. Polyunsaturated and saturated fatty acid ratio known as P/S value. The fats having P/S value more than 2 are generally recognised as hypocholesterolemic.

The mechanism of lipid lowering effect of polyunsaturated fatty acid is not clear. Sheoherd et al (1980), Turner et al (1980) postulated that, it increases in the clearance and decrease synthesis of LDL in normal individual.
AIMS OF STUDY
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1. To find out the basal cholesterol and other lipoproteins in Indian population.

2. To find out the day-to-day variation in serum cholesterol and other lipoprotein in healthy Indian population.