PATHOGENESIS OF HYPERLIPOPROTEINAEMIAS

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There are two ways to define normal levels of lipoproteins[1] :

i) Serum cholesterol value above the 95th percentile for a given population.

ii) Serum cholesterol value associated with significantly increased risk of coronary heart disease.

Consensus conference, N.I.H. 19852 adopts the latter values (table I).

Table 1
Definition of Hypercholesterolemia : National Institute of Health Consensus Conference on Cholesterol*

	Cholesterol, mg/dL (mmol/L)	
Age, y	Moderate Hypercholesterolemia	Severe Hypercholesterolemia
20-29	> 200 (5.17)	> 220 (5.69)
30-39	> 220 (5.69)	> 240 (6.21)
≥40	>240 (6.21)	>260 (6.72)

*JAMA 1985, 253, 2080-90

Patterns of lipoproteins in plasma (Lipoprotein Types, Frederikson and Levy[3] and W.H.O. Committee) are given in Table 2.

The exogenous pathways for their metabolism (Fig. 1) begins with chylomicron absorption from the intestine. In the adipose tissue and muscle, the chylomicrons are hydrolysed, with the liberation of free fatty acids and the chylomicron remnants which are removed from the circulation by hepatic receptors. The liver incorporates the contained cholesterol into bile acids and other necessary body constituents and also secretes very low density lipoproteins (VLDL), the triglycerides are also hydrolysed in the adipose and muscle tissue. The remnants (intermediate density lipoproteins-IDL) circulate in the blood, to be taken up by hepatic receptors which also take up the low density cholesterol rich LDL for degradation.
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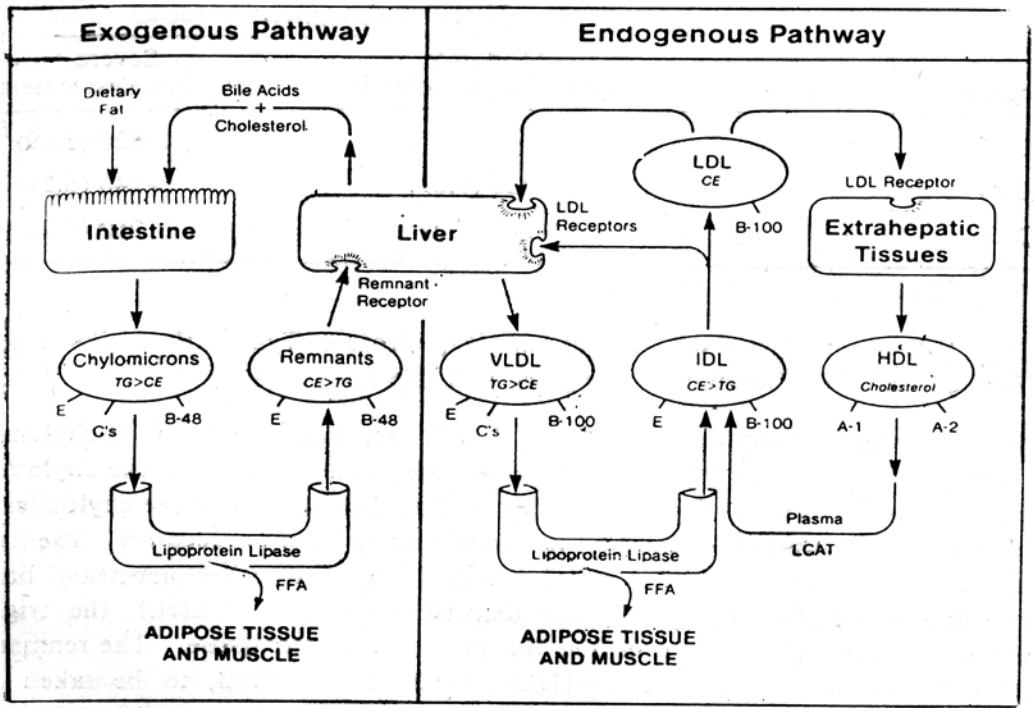
Table 2

Patterns of lipoprotein elevation in plasma (lipoprotein types)

Lipoprotein	*Major elevation in plasma*	
pattern	*Lipoprotein*	*Lipid*
Type-1	Chytomicrons	Triglycerides
Type-2a	LDL	Cholesterol
Type-2b	LDL and VLDL	Cholesterol and triglycerides
Type-3	Remnants	Triglycerides and cholesterol
Type-4	VLDL	Triglycerides
Type-5	VLDL and chylomicrons	Triglycerides and cholesterol



The extrahepatic tissues too have LDL receptors and take up cholesterol for cell wall synthesis, etc. This cholesterol, set free as cells disintegrate, then circulates as high density lipoproteins (HDL). So HDL arises in plasma as the

Table 3

The major primary forms of hyperlipoproteinaemia

* All of the monogenic disorders are autosomal, R=recessive, D=dominant.
\+ X=xanthomas : P=pancreatitis :A=premature atherosclerosis.

Disorder and Pattern of Inheritance*	Biochemical Defect	Plasma Lipoprotein Elevation	Proposed Mechanism	Typical Plasma Lipid Concentrations *T=Triglyceride C=Cholesterol (mg/dl)*	Typical Clinical Findings*
Monogenic					
Familial lipoprotein lipase deficiency : R	Deficiency of lipoprotein lipase	Chylomicrons	Decreased hydrolysis of triglycerides in chylomicrons	T: 10,000 C: 500	X.P
Familial type-III hyperlipoproteinemia (dysbetalipoproteinemia) : R**	Abnormal form of apo E	Chylomicron remnants and IDL	Decreased catabolism of chylomicron remnants and IDL	T : 350 C : 350	X.A
Familial hypercholesterolemia (heterozygous form) : D	Deficiency of LDL receptor	LDL	Decreased catabolism of LDL.: decreased catabolism of IDL with increased conversion to LDL.	T : 100 C : 350	X.A

** Requires homozygosity for apo-1; abnormality plus additional factor (s) for clinical expression.

(Table Contd.)

(Table 3 Contd.)

Familial hypertriglyceridemia: D	Unknown	VLDL (rarely chylomicrons)	Decreased catabolism or increased production of VLDL	T : 500 C : 200	X.A.P
Multiple lipoprotein-type hyperlipidemia (familial combined hyperlipidemia) : D	Unknown	VLDL and LDL (rarely chylomicrons)	Increased production of VLDL	T : 100-500 C : 250-400	X.A.P
Multifactorial					
Polygenic hypercholesterolemia : complex	Unknown	LDL	Unknown	T : 100 C : 280	A
Hypertriglyceridemia : complex	Unknown	VLDL	Unknown	T : 500 C : 200	—

Table 4

The major secondary forms of hyperlipoproteinaemia

Disorder	Plasma Lipoprotein Elevation	Proposed Mechanism	Typical Plasma Lipid Concentrations *T=Triglyceride C=Cholesterol (mg/dl)*	Typical Clinical Findings*
Diabetes mellitus	VLDL (occasionally chylomicrons)	Increased secretion and delayed catabolism of VLDL	T : 300-10.000 C : 200-3000	X.P.A
Hypothyroidism	LDL	Decreased catabolism of LDL, owing to suppressed LDL receptors	T : 100-400 C : 300-400	A
Nephrotic syndrome	VLDL and LDL	Increased secretion of VLDL and LDL: decreased catabolism of VLDL and LDL	T : 100-500 C : 300-500	A
Uremia	VLDL	Decreased catabolism of VLDL	T : 300-800 C : 200-300	A
Primary biliary cirrhosis	Lipoprotein X (↑ cholesterol and phospholipid)	Diversion of biliary cholesterol and phospholipids into blood stream	T : 100 C : 300-2000	X.A
Alcoholic hyperlipidemia	VLDL (usually chylomicrons)	Increased secretion of VLDL in individuals genetically predisposed to hypertriglyceridemia	T : 300-10.000 C : 200-300	X.P
Oral contraceptives	VLDL (occasionally chylomicrons)	Increased secretion of VLDL in individuals genetically predisposed to hypertriglyceridemia	T : 300-10.000 C : 200-300	X.P

* X = xanthomas : P = pancreatitis : A = premature atheroscleosis.

end-product of several processes. High density lipoprotein (HDLs) may accept cholosterol from extrahepatic tissues (and other sources) and transfer it to VLDLs (and LDLs) and cholesterol carried on these latter lipoproteins can be removed by the liver. HDL is like a shuttle for cholesterol accepting it from tissues and transferring it to VLDL. In the circulation, cholesterol is converted to ester form by plasma enzyme lecithin cholesterol acyltransferase LCAT. This is subsequently removed by the HDL and LDL for synthesis of cell membrane or taken to the liver for exeretion as biliary cholesterol or bile salts. Chylomicron, VLDL, LDL system constitute the transport system for cholesterol of both dietary and endogenous origin.

Metabolic abnormalities can occur at almost all levels to produce hyper-lipoproteinaemia. From single gene defects of strong penetrance and autosomal, mostly dominant transmission, to those with weak penetrance, needing genetic defects at multiple levels and additional acquired, environmental factors. Table III outlines the major primary forms of hyperlipoproteinaemias. Clinically, hyperlipoproteinaemias are found also secondary to other more dominant clinical disturbances e.g. diabetes mellitus, hypothyroidism, nephrosis, biliary cirrhosis etc. Diet often plays an important role in the so called polygenic or multifactorially determined disorders. Naturally the latter are far Gommoner (Table IV).

Significantly high cholesterol level in plasma is found in 5% of healthy western population, Amongst every 20 such persons only one has heterogenous Type 2a, two have the mixed type with high triglyceride levels as well and the remaining seventeen would have the multifactorial type or polygenic type of hypercholesterolaemia. Whereas upto 50% of lst degree relatives are affected in the single gene type defects, only 10% are so affected in the multifactorial type. In the Seattle study[4] of 500 survivors of myocardial infarction, 33 % had hyperlipoproteinemia. Below 50 years of age, 50% of males and 66% of females were so affected. But above 70 years of age, only 25% of females had hyperlipoproteinemia while no males had it. More than half of this population had simple monogenie disorders, more often high triglycerides than cholesterol. Whereas polygenic disorders were equally common at all ages, monogenic disorders were `commoner below 60 years, as expected, since simple genetic abnormalities accelerate changes with age.

In the monogenic mixed type (high triglyceride and cholesterol, Types IIb and III) of hyperlipoproteinaemias, the lipid levels vary with time and may be normal in between, and triglyceride and cholesterol may be raised singly or together at other times. Presence of diabetes mellitus or other diseases have additive effect. It is thought that the hyperinsulinemia associated with age related adiposity raises VLDL levels (and as a consequence LDL levels) and may thus in part be responsible for the age related rise in lipid levels seen in the western population.

Role of hypertriglyceridaemia in causing atherosclerosis is disputed and is problematic since cholesterol levels are also raised at the same time. However, if other family members have raised cholesterol levels, ischemic heart disease is, enhanced in the subset with only raised triglyceride[4].

High density cholesterol levels largely follow LDL and VLDL levels inversely. If HDL forms atleast 20% of total cholesterol in plasma, atherogenic potential is lessened as it is in the female. HDL levels are governed by, apart from sex, gene, exercise and also alcohol intake. The last two raise the HDL level. Since the normal range of HDL level is narrow, laboratory error, which is common, reduces its importance in the individual. Occasionally, marginally high LDL loses its significanae when HDL is high.

Though genetic factors contribute significantly for many cases of primary hypercholesterolaemia, diet has a major role in this causation.

Total calories, saturated fatty acids and dietary cholesterol can raise the LDL levels higher in some people than others and this may be due to absorptive or metabolic differences.

The relationship of diet composition is important from the public health point of view since dietary management is simple, though difficult to impose. Surprising it may seem, but the fact is that the impact of diet on cholesterol levels is still not completely elucidated. In metabolic experiments, raising cholesterol intake from 250 to 500 mg daily, raises plasma cholesterol, on an average, by 10 mg. But the effects are variable. A single large intake has more effect than when the same amount is instituted over number of meals. Also, dietary cholesterol may induce formation of other species of lipoproteins, atleast in the post-prandial state, and the overall atherogenic effect could be more than what is apparent from its effect on fasting plasma cholesterol level.

For each 1% of total energy intake supplied as saturated fatty acid, the plasma cholesterol rises by 2.7 mg%. HDL level does not change. Shorter chain fatty acids raise LDL level more. Mono-uusaturated fatty acids, typified by oleic acid are neutral in their effect on plasma cholesterol. The omega-6 polyunsaturated fatty acids, typified by linoleic acid, lower cholesterol level by 1.35 mg% for each 1 % of energy intake substitution (in exchange for mono-unsaturated acids), but a higher intake, nearing 20%, lowers HDL level and may have other harmful effects. The omega-3 poly-unsaturated fatty acids, found in fish oils, inhibit synthesis of triglycerides. The effect on cholesterol is same as that of oleic acid. The overall effects of high intake on multiple organ systems are unknown, though Eskimos seem to do quite well.

The carbohydrate content of diet is neutral in its effect on plasma cholesterol level. High intake raises triglyceride level, but the effect is often transient. The HDL level is lowered, clinical significance of which is not known. Further, the effect on triglyceride is related to the caloric status. In overweight individuals, the level can rise substantially, whereas in lean people, there is no such effect.

High total energy intake in people already obese raises the triglyceride and sometimes cholesterol level and lowers HDL level. Apart from acute effects in metabolic experiments, there are long term effects of high cholesterol and saturated fatty acids consumption in that there is incremental effects on plasma cholesterol with a constant intake. This may be another mechanism of age related rise in plasma cholesterol. Also the population differences in plasma cholesterol, not explained by dietary cholesterol differences at the time of study, may thus be explained. Dietary cholesterol has also been found to be an independent risk factor for atherosclerosis, apart from its effect on plasma cholesterol. There may also be other direct and indirect effects enhancing atherosclerosis.

The observed paradox in some studies that a 20% fat diet fails to lower the plasma cholesterol as expected, is not explainable. It is as if the level is self-sustaining. Furthermore, with very low fat diets, VLDL levels rise and the HDL levels become reduced, an undesirable situation.

Physical exercise is complex in its effects on plasma cholesterol level. Most effect is through VLDL level which is lower in people habitua1ly engaged in physically active occupations and recreation activities.

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