Lipoprotein disorders in non-insulin-dependent diabetes mellitus

P Shah, M.G. Karmarkar

ABSTRACT

We describe the classification and functions of major apoproteins and relationship of atherogenesis to major lipoprotein subtypes. The abnormalities of lipoproteins in NIDDM are described with goals of treatment and the strategies required to achieve the described goals.

INTRODUCTION

Lipoprotein are made up of lipids (triglycerides, esterified cholesterol), phospholipids and apoproteins. Latter are specialised molecules with varied roles from stabilisation of otherwise non-polar lipids in circulation to metabolism of these molecular complexes. Though these complexed proteins form a continuum of molecules varying in size, density, function and composition, these have been classified as depicted in Table 1 (1).

Triglycerides and cholesteryl esters form the core of lipoproteins, and the free cholesterol, apoproteins and phospholipids form the surface.

Apoproteins are the surface proteins of the lipoprotein complexes. The functions of major apoproteins are shown in Table 2 (1).

The dietary lipids are converted to fatty acids and free

Table 1: Classification of apoproteins

Lipoprotein	Density	Mol Wt. ($\times 10^6$)	Diameter (nm)	Major lipid content
Chylomicrons	0.95	400	75- 1200	Triglycerides
VLDL	0.95-1.006	10-80	30-80	Triglycerides
IDL	1.006-1.019	5-10	25-35	Triglycerides+Cholesterol+Phospholipids
LDL	1.019-1.063	2.3	18-25	Cholesterol+Phospholipids+Triglycerides
HDL	1.063-1.21	0.17-0.36	5-12	Phospholipids+Cholesterol+Triglycerides

Table2. Functions of major apoproteins

Apoproteins	Lipoproteins	Metabolic Functions
Apo-A-1	HDL, Chylomicrons	LCAT** activator, Structural component of HDL
Apo-B-100	VLDL, IDL, LDL	Formation, packaging and secretion of VLDL LDL receptor ligand. Structural protein of VLDL, IDL, LDL
Apo-B-48	Chylomicrons	Formation, packaging and release of chylomicrons
Apo-C-II	All	Activator of LPL*
Apo-C-III	All	Inhibitor of LPL*
Apo-E	All	Ligand for LDL receptor binding for several lipoproteins

*LPL = lipoprotein lipase, **LCAT=Lecithin cholesterol acyl transferase

From: Department of Endocrinology, Metabolism and Diabetes, All India Institute of Medical Sciences, New Delhi-110 029, India

cholesterol in gut, and are reconstituted to form triglycerides and cholesteryl esters in the enterocytes. Here, Apo B-48 helps packaging and secretion of these newly formed chylomicrons. These chylomicrons while traversing the thoracic duct and the vena cava acquire Apo C-II, Apo C-III and Apo E, and, phospholipids and free and esterified cholesterol from HDL. Apo C-II activates the lipoprotein lipase at the luminal surface of capillary endothelium and chylomicron triglycerides are hydrolysed. Phospholipids, Apo C-II and Apo C-III are transferred back to the HDL and the remnant are picked up by the liver cells through a process involving Apo-E and hepatocyte cell surface receptor(s) (2).

Endogenous triglycerides produced in hepatocytes are packaged with some phospholipids and cholesteryl esters to form VLDL in presence of Apo-B-100. Like chylomicrons VLDL also acquire Apo-C-II, Apo-C-III, and Apo E while in circulation. Also like chylomicrons, VLDL triglycerides are hydrolysed by activation of LPL by Apo-C-II, and, surface cholesterol, phospholipids and apoproteins are transferred back to HDL. In process IDL is generated. Apo-E mediated hepatocyte uptake of IDL and hepatic triglyceride lipase (HTGL) mediated hydrolysis help in uptake of VLDL from plasma and conversion of VLDL and IDL to LDL on the luminal surface of endothelium of hepatic sinusoids. This process reduces the triglyceride content of these particles, and LDL are thus essentially cholesteryl-ester-rich Apo-B-100 containing lipoproteins. The uptake of LDL is mediated mainly (60-70%) by the LDL receptors (liver: 40-60%; Adrenals and other tissue) in presence of Apo-B-100 acting as the ligand for the receptor. On internalisation of the receptor ligand complex the cholesteryl esters are hydrolysed by the lysosomal enzymes and the free cholesterol released in the cytoplasm seem to play a regulatory role on LDL receptor turn over (2).

Apo A-I, apo A-II, apo A-VI and apo E with lecithin cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP) form the nascent, flat, discoid, HDL in liver, blood, lymph and intestines. These HDL3 particles pick up free cholesterol released from the cell surface/dying cells. LCAT esterifies (apo-A-I acting as a cofactor) these into cholesteryl esters and these are taken up by the hydrophobic core of the HDL particles ballooning them into spherical particles. These are now capable of taking up apo-C-II and apo-C-III released from VLDL and chylomicrons and in process getting converted into HDL2. Apo C-II apo C-III and apo-E are transferred to VLDL and chylomicrons. The cholesteryl esters in these particles can have one of the three fates:

1. transfer to VLDL or chylomicrons by CETP and then taken up by the liver.
2. transfer to the cells while the particles remain on the cell surface.
3. apo-E induced LDL-receptor/apo-E-receptor mediated internalisation in the hepatocytes (1).

ATHEROGENESIS AND LIPOPROTEIN SUBTYPES

Monocyte derived macrophages at the vessel wall take up chylomicrons and remnants leading to cholesteryl ester accumulation. A higher level and longer persistence in circulation of chylomicrons/remnants, like when LPL activity is deficient (in diabetes mellitus), when VLDL is high (as it would compete with it), or when dietary cholesterol and saturated fats are high (leading to high chylomicron synthesis, VLDL production, and LDL receptor down regulation with reduced clearance of chylomicrons) it is likely to cause accelerated atherosis.

Apo-B-100 containing VLDL, IDL and LDL have been extensively shown to correlate with the risk of coronary artery disease (CAD). But the mechanism of atherogensis is still under close scrutiny. VLDL unless cholesteryl ester rich, does not seem to be taken up by the macrophages and smooth muscle cells in vitro. Thus it is postulated that the cholesteryl rich VLDL or IDL

Table 3: Lipoprotein abnormalities in Diabetes

Reduced	LPL (insulin dependent enzyme)	Increased VLDL, Chylomicrons, IDL, + reduced HDL
Reduced	HTGL	Reduced HDL + increased IDL
Increased	VLDL production (due to increased flux of FFA)	High VLDL
Reduced	LDL receptor activity (insulin plays a role in receptor activity and turnover	High LDL
Glycation	of lipoproteins especially LDL	High LDL
Oxidation	of LDL	High LDL

Table 4: Treatment groups based on categories of European Atherosclerosis Society (16).

Group	Diagnostic Levels (mg/dL)	Management
A	Cholesterol 200-250	Restrict calories if overweight, lipid lowering diet and correct glycemic status & other risk factors if present, reassess in 6 months.
B	Cholesterol 250-300 Triglyceride <200	Restrict calories if overweight, prescribe lipid-lowering diet and monitor response and compliance; if cholesterol remains high reinforce diet; if this fails, consider lipid-lowering drug therapy.
C	Cholesterol <200 Triglyceride 200-500	Restrict calories if overweight, prescribe and monitor lipid-lowering diet; correct other risk factors if present.
D	Cholesterol 200-300 Triglyceride 200-500	Restrict calories if overweight, correct underlying causes of high triglyceride if present; prescribe and monitor lipid-lowering diet; correct other risk factors if present; if lipid response is inadequate and overall CAD risk is high, consider use of lipid-lowering drugs.
E	Cholesterol >300 Triglyceride >500	Correct underlying causes; prescribe lipid lowering diet; control other risk factors; if treatment goal not achieved, prescribe drug therapy.

contribute to the risk of CAD in hypertriglyceridemia. LDL rich in triglycerides (Tg) are atherogenic (compared to the normal variety) and this sub-population of Tg is responsible for the risk of CAD in hypertriglyceridemia. Abnormal apo-B-100 of this sub-population and certain other changes in LDL (lipid peroxidation) lead to a poor binding to the LDL receptor and accumulation in the circulation. These abnormal LDL become ligands for scavenging and the scavenger cells become 'foamy'.

HDL is negatively correlated with the risks of CAD. HDL also is negatively correlated with the VLDL, IDL and LDL; thus the negative correlation with CAD is explicable. However, a decreased HDL carrying capacity of the cholesteryl esters would make it available for the vessel wall and atherogenesis.

LIPOPROTEIN ABNORMALITIES IN NIDDM

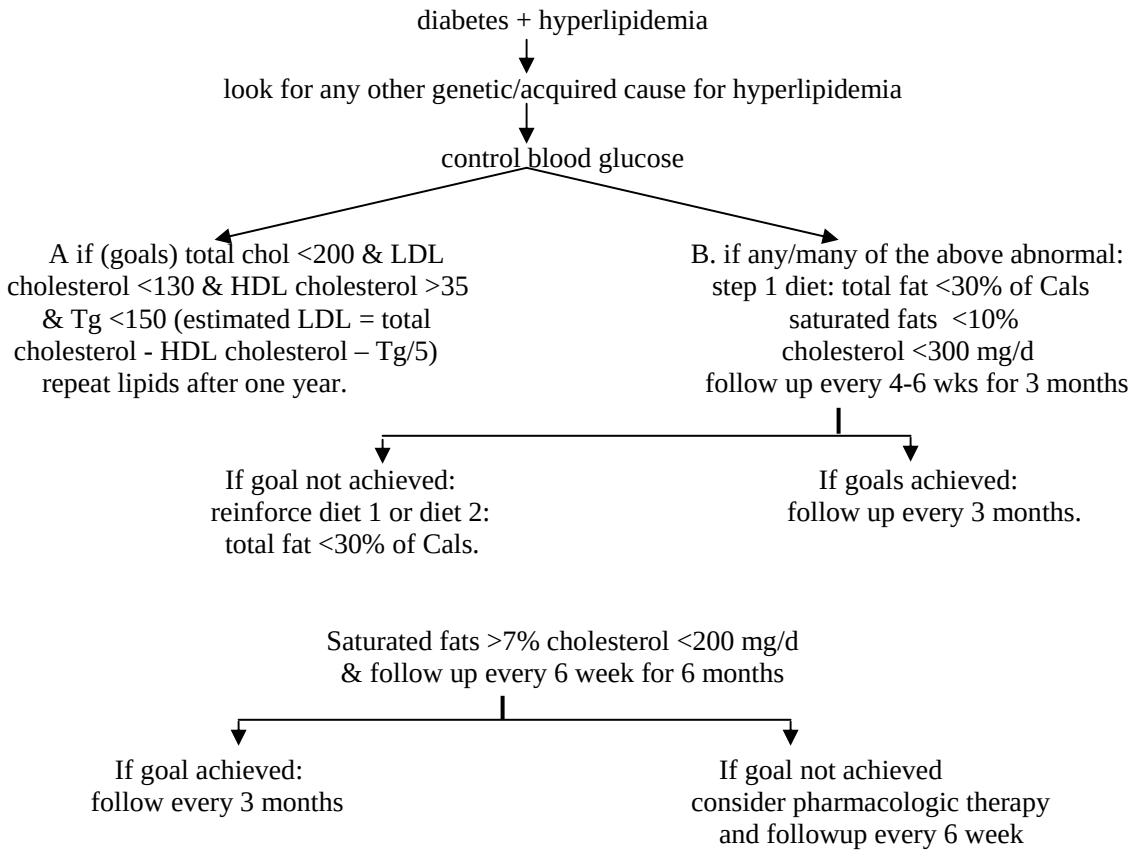
Type of lipoprotein abnormalities in diabetes depend on many factors, type of diabetes, endogenous insulin reserve, degree of obesity and insulin resistance, type of therapy, degree of glycaemic control, and the presence or absence of nephropathy (3).

The most frequent serum lipid abnormality in NIDDM is an elevation of serum triglycerids to 1.5 - 3.0 times the sex, age and body weight matched non-diabetic controls. In a study of 507 NIDDM patients from Delhi about 50% subjects were found to have > 150 mg/dL triglycerides. Reduction of HDL cholesterol (by 10-20%), primarily due to the fall of HDL2 cholesterol is also seen in NIDDM (4). Due to a reduced concentration of apo A-1 also, cholesterol/apo A-1 ratio is low (5). Though the LDL metabolism is abnormal NIDDM patients seldom manifest increased levels of serum total and LDL cholesterol. Despite this, many NIDDM patient exhibit an increase in apo B levels (4, 6). The levels of VLDL Tg, LDL cholesterol and apo-B correlate directly with the glycemic control; however, the HDL cholesterol levels do not.

The onset of dyslipidemia seen in NIDDM is as early as the onset insulin resistance. This is more so because of the associated obesity in this group. Another interesting finding in obese NIDDM is the obliteration of difference of HDL and LDL levels between the two sexes. With a worse effect on the LDL and HDL in females, the finding that the difference between the incidence of CAD in two sexes also gets obliterated is explicable. (7, 8).

The control of blood glucose over a period of time (three months) normalises the diminished post-heparin LPL and the lipid abnormality in those who have no associated primary hypertriglyceridemia. (9). It has been conclusively shown that reducing LDL cholesterol and increasing the HDL cholesterol are beneficial in reducing CAD risk, with lowering of LDL cholesterol (despite 'normal' levels) a primary target in the prevention of CAD (8). Since the commonest defects in NIDDM are elevated serum triglycerides and reduced HDL cholesterol normalising these two are important therapeutic goals. The data from WHO Multinational Study on the complications of diabetes indicate that elevation of the serum triglyceride level is a risk factor for major vascular events in diabetics (11, 12).

Table 5: Management of diabetes with hyperlipidemia (Modified from 7)



TARGET VALUES OF SERUM LIPIDS IN NIDDM

The National Cholesterol Education Programme (USA) have drawn guidelines for control of lipoproteins in population in order to reduce the coronary risk, however the tighter levels of control are required in all males (the two risk factors: male sex, diabetes) and all female diabetics with severe obesity or hypertension (13). Thus the goal of LDL control would be 130mg/dl in males and 160mg/dl in uncomplicated female diabetics. However, the goal for female diabetics should also be same as for male diabetics as the sex differential for CAD incidence is obliterated. (7). Because of the specific features of lipid abnormalities in diabetes, the European NIDDM Policy Group has included not only cholesterol levels but also serum triglycerides and HDL cholesterol as therapeutic target (14). Garg and Grundy have recommended that total cholesterol be kept < 170 mg/dl since prevalence of CAD is low in diabetic populations with cholesterol values in this range (15). The optimal values for serum triglycerides and HDL cholesterol remain arbitrary.

It is recommended that the serum lipids (serum Tg, Total cholesterol and HDL cholesterol) be measured once at the time of first visit and then annually, and, whenever the glycemic control is poor (serum Tg and total cholesterol). If the levels are elevated and/or lipid-lowering therapy initiated, measurements should be repeated every 3 months until the levels have become stable.

DIABETIC CONTROL AND LIPID ABNORMALITIES

If despite good diabetic control (which indeed should be a prime target) the patients have abnormal lipid values, then the necessary actions are the same as for non-diabetic high-risk patients.

Some features are unique to the management of hyperlipidemias in diabetics.

1. The decreased intake of fats implies an increase in carbohydrate intake (as the protein intake cannot be increased due to the fear of inducing/exacerbating nephropathy).

2. The increase in dietary fiber associated with the carbohydrate intake is a good LDL cholesterol lowering agent.

3. Omega 3 fatty acid containing fats (fish oils) though associated with a decreased risk of cardiovascular mortality in diabetics may lead to a deterioration in glycemic control. There is some evidence that the omega 3 fatty acid containing triglycerides may have an adverse effect on HDL and even LDL cholesterol. Hyperglycemia may require increased insulin doses with possible adverse effects on lipids.

4. Bile acid binding derivatives increase Tg, and the gut symptoms may be severe in those already having autonomic neuropathy. Nicotinic acid tends to worsen the glycemic control, with an increased requirement of the insulin. Gemfibrozil (fibric acid) is a good drug for hypertriglyceridemia, but not good for hypercholesterolemia alone. Lovastatin (HMG CoA reductase inhibitor) is effective in diabetics, lowering cholesterol and Tg by about 20%. Gugulipid (gum gugul) is also an effective drug for reducing both the serum triglycerides and cholesterol.

5. Weight control helps in control of diabetes and dyslipidemia both.

CONCLUSIONS

Hypertriglyceridemia (VLDL) is commonly associated with uncontrolled diabetes. Variety of minor changes in other lipoproteins, not detectable by estimation of their 'values' seen to be all too important for atherogenesis. Hyperlipidemia associated with diabetes markedly and extensively predispose the person to the risks of CAD. A vast majority of diabetics with hyperlipidemia are unaware of their lipid status (17) and still less are given treatment. In order to prevent the extensive coronary artery involvement by atherosclerosis (18) in diabetics it is imperative to pay adequate attention to associated dyslipidemias.

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