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Diabetes Mellitus and Dyslipidemia

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Diabetes is commonly associated with abnormalities in plasma lipids and lipoprotein levels commonly referred to as "Dyslipidemia". About 50% of all diabetic patients have dyslipidemia. Lipid abnormalities are more common in type 2 diabetes than in type 1 diabetes. Insulin is an anabolic hormone having widespread influence on various processes which are growth enhancing and beneficial to the organism. Insulin exerts profound influence on expression and activity of genes regulating various key enzymes involved in lipid metabolism as well as synthesis and expression of apolipoproteins both in the liver and peripheral tissues (adipocytes, skeletal muscle, endothelial cell, fibrocyte, etc). In the peripheral bed at the endothelial tissue interphase, it enhances the lipolytic enzymes (lipoprotein lipase = LPL) and enhances the clearance of very low-density lipoprotein (VLDL) and chylomicrons. These triglyceride (TG) rich lipoproteins break down to liberate free fatty acids (FFAs) and glycerol. While FFA is used as the main source of energy in the postabsorptive state, glycerol is recycled back to the liver. In the process of hydrolysis of fat, mono and diglycerides are also liberated at these sites.

Levels, composition, size and metabolism of plasma lipoproteins in subjects with diabetes mellitus (DM) are influenced by factors such as:

1. Type of diabetes mellitus
2. Habitus i.e., lean, standard weight and obese
3. Nutritional status: Under nourished or well nourished
4. Insulin sensitive or resistant stage
5. Glycemic status and type of treatment
6. FFA influx to the liver vis-a-vis insulin level in portohepatic bed
7. Presence of complications like nephropathy.

Table 1. Order of priorities for treatment of diabetic dyslipidemia in adults.

LDL cholesterol lowering

- First choice: HMG CoA reductase inhibitors (statin)
- Second choice: Bile acid sequestrants (Resin) or nicotinic acid

HDL cholesterol raising

- Weight loss, increased physical activity, stopping of smoking
- First choice: Fibrates or nicotinic acid
- Second choice: Statins

Triglycerides lowering

- Good glycemic control
- Fibric acid derivatives (fenofibrate, gemfirozil)
- Some statins in high doses

Combined hyperlipidemia

- First choice: Good glycemic control and statins
- Second choice: Good glycemic control and statins and fibric acid derivatives (gemfibrozil, fenofibrate)

Broadly the lipid abnormalities (dyslipidemia) seen in type 1 and type 2 diabetes are presented in Table 1. Hypertriglyceridemia is the common dyslipidemia seen in uncontrolled diabetic state, insulin resistant stage and in presence of nephropathy in type 2 diabetics. Table 2 depict the influence of nutritional status and glycemic control in patients with type 2 diabetes. Again, in Indian diabetics hypertriglyceridemia with increased VLDL is more common dyslipidemia than low high-density lipoprotein (HDL) cholesterol levels. This is very likely due to over production of VLDL by the liver.

VLDL is endogenous in origin and thus the dyslipidemia is type IV hyperlipoproteinemia. Therefore hypertriglyceridemia is consequent to both over production by liver and poor clearance of VLDL in the peripheral tissues due to inappropriate action of LPL.The suppressed activity of LPL is because of the insulin resistant or insensitive state in metabolically uncontrolled diabetics. With adequate glycemic control and maintenance of euglycemia it reverts to near normal levels. Therefore presence of hypertriglyceridemia is a good indicator of the state of poor metabolic control in patients with DM. Alterations in cholesterol levels are not uniform in patients with DM. In the diabetics of the West as well as affluent populations of our country, a rise in cholesterol levels along with TGs is seen, so in such patients, the type

Table 2. Types of lipid abnormalities in DM.

Type 1 DM		
Usual level of glycemia (euglycemia)	:	Similar to non-diabetics
Poor glycemic control	:	TGs level and high LDL cholesterol oxidation
Diabetic nephropathy	:	High LDL cholesterol & Lp(a), intermediate HDL cholesterol
Type 2 DM		
Usual levels of glycemia (euglycemic)	:	HighTG, intermediate HDL cholesterol, prevalence of small dense LDL, highLDL susceptibility to oxidation
Poor glycemic control	:	Worsening of hypertriglyceridemia
Diabetic nephropathy	:	High TG, High Lp(a) , Intermediate HDL

of hyperlipoproteinemia is type IIb. However diet, nutritional status and anthropometry play a vital role and the picture is different in most of our diabetics. Even in an uncontrolled state, only about one fourth of diabetics reveal hypercholesterolemia.

The role of FFAs and lipotoxicity in the pathogenesis of type 2 diabetes:

Increased circulating concentrations of non-esterified fatty acids or FFA and TGs are associated with the development of insulin resistance and type 2 diabetes, in genetically susceptible persons. It is proposed that in uncomplicated obesity, increased lipid availability induces both hyperinsulinemia and insulin resistance in a parallel fashion, thereby maintaining normoglycemia. A further increase in substrate overload leads to impaired β-cell compensation and hyperglycemia appears.

Another hypothesis is that the fat laden islets undergo an accelerated rate of apoptosis and this play a part in the β-cell failure. An accumulation of TGs in the skeletal muscle or the increased availability of fatty acids provides an alternate energy source (to glucose) and this results in decreased glucose utilization resulting in hyperglycemia.

LIPID PROFILE IN INDIAN POPULATION

Interpretation of dyslipidemia in diabetics has to be done keeping in view the lipid normogram of the inherent population. The national lipid normogram is presented in Table 3.

Population based studies on lipid profiles, done at our center showed that the TGs levels had a U shaped distribution in upper, middle and lower socio-economic groups (SE groups), respectively. While the higher TG levels in the upper SE group is very likely to be due to higher fat intake compounded with slower VLDL clearance, relatively higher levels in the lower SE group is mostly due to very high carbohydrate diet. Interestingly, analysis of lipid profile done in persons living in a geographical area of 10 kilometers radius but belonging to different ethnic groups as well as having different lifestyle and food habits revealed significant differences in the lipid profiles, as shown in Table 4. The fishermen (Naulia) had the most ideal lipid profile to be followed by tribals where the cholesterol profile was ideal but TG levels were similar to urban elite population. The fishermen were physically most active, consumed on an average 500 g of fish per day while the tribals were nutritionally deprived with poor protein intake. Both these communities were on high carbohydrate diets while the Urbanites had more refined carbohydrate food, richer in both fat and proteins. This further confirms that

Table 3. Lipid profile in controls, untreated and treated UND and WND. Type 2 diabetics (mg%).

Sub	TG	Total chol	HDL-C	LDL-C	VLDL-C
Untreated UND	157.1	283.4	63.6	158.8	64
Treated UND	107.8	199	70.4	104.6	24
Control	95.3	216.4	68.7	131.2	16.5
Untreated WND	168.4	300.2	52.8	182.2	65.2
Treated WND	123.2	230.2	67.3	136.2	26.7

Das, Tripathy, Samal and Panda. Diabetes Care, 1984.

high carbohydrate diet had a great influence in modulating TG levels vis a vis physical activity in our populations. The national lipid normogram again reflects the influence of inherent dietary pecularities on the lipid profile of people from east, west, north and south zones of India.

Table 4. Lipids and lipoprotein cholesterol normograms in Indians (mg%).

Zone	Triglycerides	Total Cholesterol	HDL-C	LDL-C
East	115	185	42	115
South	(a) 155	180	38	107
	(b) 119	172	40	108
West	107	188	38	129
North	132	150	43	101

Based on population studies as reported from different parts of India Sidhartha Das and V. Mohan,Chapter on Lipids, API Text Book of Medicine, 7th Edition, 2003

LIPID LEVELS AND THEIR INTERPRETATIONS IN DIFFERENT TYPE OF DM (TABLE 5)

Type 1 DM: This is a typical situation where insulin production is minimal to nil and therefore its concentration is low both in the porto-hepatic circulation and peripheral blood. The lipoprotein composition is accordingly affected with low high-density lipoprotein cholesterol (HDL-C), poor esterification of cholesterol, more of TG with less VLDL clearance. This is more so in inadequately treated patients with poor glycemic control. The activity of enzymes like lecithin cholesterol acyl transferase (L-CAT) and lipases are suppressed due to low circulating insulin levels. This adversely affects HDL metabolism. Besides, higher concentration of free cholesterol in low-density lipoprotein (LDL) and intermediate density lipoprotein (IDL) makes them more atherogenic. However, institution of insulin treatment and maintenance of euglycemia rapidly reverses lipid metabolism to normal.

Type 2 DM: In patients with type 2 DM there is global dysfunction of lipoprotein metabolism. The degree of dyslipidemia is more widespread (Table 1). There is increase in small dense LDL (LDL3) which is highly atherogenic. In patients with poor glycemic control, levels of TG rich lipoproteins are higher. This rise is not only due to over production of VLDL but also poor peripheral clearance consequent to lesser expression of ApoB100 receptors on endothelial cell surface. In uncontrolled patients with type 2 DM the recycling of receptors is also slow. Glycated ApoB100 have longer interaction with its receptors and so prolongs the half life of both LDL and VLDL molecules. The HDL levels may not be low in these type of diabetic subjects, more so with fair glycemic control. Unlike type 1 DM, patients with type 2 DM have good insulin reserve and so much higher porto-hepatic insulin concentration which keeps the HDL cycle and hepatic enzyme system at an optimum. Patients with poor peripheral insulin levels may therefore have near normal HDL cholesterol levels while values of VLDL cholesterol, LDL cholesterol, IDL cholesterol and TG may be higher. Such

discordance is peculiar to type 2 DM. Type IV type IIb and type III dyslipoproteinemias commonly met with in type 2 DM often reverses with diet and hypoglycemic drug therapy.

Table 5. Lipid profile in tribals, fishermen and urban elite population in mg/dl.

Sub	HDLs	LDLs	VLDLs	TC	TG
Urban	41.8	114.8	28.8	185.4	144.4
Fishermen	43.5	71.4	24.8	139.8	124.2
Tribals	33.6	70.9	28.9	133.5	144.9

Mondal, Das, Mohanty et al. Jr. Nutr. Med. 1994.

Low body weight type 2 DM (lean type 2 DM): The diabetic state differentiates lean type 2 DM from PEM in many respects including lipid profile. Cholesterol content in LDL and VLDL are higher as is TG content, although the absolute values of these lipid levels are much lower than in well nourished diabetics (WND). Levels of mean HDL-C is visibly higher in lean type 2 DM irrespective of glycemic status. The TG levels in Indian subjects with DM is higher both in lean type 2 DM as well as in WND when compared with data from the west. This profile is likely to be the true reflection of the influence of nutritional status lipid profile in developing societies rather than a consequence of any specific biological alterations.

Studies done by Seshiah, et al. from Chennai had also revealed similar alterations in the lipid profile in obese, non-obese and lean diabetics in their population. While in the WND there was a positive correlation suggesting slower removal of TG in the obese, there was no correlation in the lean type 2 DM. Studies on lean type 2 DM have shown that pre-existing dyslipidemia found in an uncontrolled state improves with establishment of glycemic control. Hypercholesterolemia is very unusual in such lean patients with DM.

It is a well established fact that hypertriglyceridemia and TG content of muscle bears a negative relationship to whole body insulin sensitivity. The patients with type 2 DM invariably have serious breakdown in lipid dynamics often reflected as elevated levels of FFA and TG together with excessive deposition of fat in various tissues including muscle bed. The high FFA levels adversely effects insulin mediated glucose disposal in peripheral blood. Such FFA arises from hydrolysis of TG. In peripheral circulation. Therefore TG is considered to be a surrogate marker for fatty acids in general. Levels of long chain fatty acids and their derivatives increase in states of insulin resistance (obesity, IGT, type 2 DM) which involves in disrupting the insulin signaling cascade and interferes with movement of glucose transporter 4 (GLUT-4) from an intracellular compartment to muscle cell surface.

In the past, high LDL cholesterol levels alone were thought to be responsible for the increased risk of CHD. It is now clear that reduced HDL-C and increased TG levels are equally important especially in diabetic patients. The association of various clusters of metabolic abnormalities with cardiovascular disease and type 2 diabetes was recognized as early as 1920. In the Framingham study, it was documented that the incidence of cardiovascular disease in diabetic men was twice than among non-diabetic men while in diabetic women, it was 3 times higher. The absolute risk of cardiovascular death has been found to be much higher in diabetic patients in the multiple risk factor intervention

Category of Risk Based on Lipoprotein Levels in Adults with Diabetes.			
Risk	**LDL**	**HDL**	**TG**
High	≥130	<40	>400
Borderline	100-129	40-59	150-399
Low	<100	>60	<150

trial (MRFIT), irrespective of the presence of other risk factors.

In the Chennai Urban Population Study (CUPS), it was noted that at every age point, diabetic subjects had a higher prevalence of coronary artery disease they also had increased carotid intimal medial thickening (a measure of generalized atherosclerosis) compared to their non-diabetic counter parts.

The prevalence of raised total cholesterol concentration in type 2 diabetes may indeed be similar to that of the general population. However, subjects with type 2 diabetes show the characteristic lipid profile of normal or slightly high LDL cholesterol with low HDL-C and mildly elevated TG concentrations. In addition, in diabetic subjects the type of LDL pattern is changed to the atherogenic small dense LDL (phenotype-B) which is much more atherogenic.

PATHOGENESIS OF ATHEROSCLEROSIS IN DIABETES

Dyslipidemia plays an important role in diabetic complications and there is a pronounced acceleration of atherosclerosis. Hyperglycemia results in formation of advanced glycation products, giving rise to reactive oxygen molecules, which activate monocytes and macrophages, causing the proliferation of vascular smooth muscle cells and thus, leading to diabetic angiopathy. One of the key actions in this cascade of events is the oxidation of the unsaturated fatty acids esterified to cholesterol in the LDL. This imparts structural changes in their apoB protein carrier and thus, the LDL binds to surrogate scavenging receptors on macrophages. LDL cholesterol accumulates in atherosclerotic plaques by association with intimal proteoglycans and thus, facilitates macrophage-foam cell conversion, endothelial deposition and smooth muscle cell proliferation.

In addition to low HDL and hypertriglyceridemia, an elevated apoB concentration is another common feature of diabetic dyslipidemia. ApoB is required for hepatic secretion of VLDL. ApoB remains associated with VLDL until it is cleared as IDL or LDL. ApoB is susceptible to glycation in diabetes which impairs its interaction with the hepatic LDL receptor and slows the clearance of LDL. Elevated apoB levels are found in almost half of normocholesterolemic patients with type 2 diabetes and are frequently associated with low HDL cholesterol levels and hypertriglyceridemia.

Diabetic dyslipidemia is considered as one component of the metabolic syndrome which is exceedingly common in persons with type 2 diabetes. It must be emphasized that abnormalities in lipids and lipoproteins represent only one among the several other factors like hypertension, hyperglycemia, insulin resistance, excessive glycation of cellular proteins, increased amount of advanced glycation end-products (AGEs), increase in proinflammatory and prothrombotic factors and cigarette smoking, all of which play a role in the pathogenesis of macrovascular complications in diabetic individuals.

Table 6. Lipid modifying drugs.

Type	Mechanism	Effect on lipid profile	Side effects
Statin Lovastatin 10-80 mg/day Simvastatin 5-80 mg/day Atorvastatin 5-80 mg/day Pravastatin 10-40 mg/day Fluvastatin 10-40 mg/day Rosuvastatin 5-40 mg/day	• Reduces hepatic cholesterol synthesis and upregulation of LDL receptors	• Reduces LDL by 40% and TG by 20% • Increases HDL by 5-10%	• Hepatitis • Myositis • GI symptoms • Lupus like syndrome
Bile acid sequestrant Cholestyramine 8-12 g b.d. or t.i.d. Colestipol 10-15 g b.d. or t.i.d.	• Binds bile acids in the intestine	• Reduces LDL by 20-30% • Increases HDL/TG	• Gastrointestinal disturbances
Nicotinic acid Upto 2 g/day	• Inhibits hepatic TG synthesis and VLDL to LDL conversion	• Reduces LDL by 15-25% VLDL by 25-35% TG by 25-85%	• Insulin resistance/ hyperglycemia • Flushing • Hepatitis • Gastrointestinal disturbances
Fibrates Fenofibrate (67-200 mg o.d.) Gemfibrozil (300-600 mg b.d.) Bezafibrate (200 mg t.i.d.)	• Inhibits hepatic • Increases fatty acid oxidation in muscle and TG hydrolysis	• Reduces TG synthesis TG by 25-40% and LDL • Increases HDL by 10-25%	• Cholelithiasis • Myositis • Liver dysfunction • Erectile dysfunction

MANAGEMENT OF DYSLIPIDEMIA IN DIABETES (TABLE 6)

Diagnosis

It is a good practice to estimate the lipid profile after achieving good glycemic control as quite often the latter by itself is sufficient to normalize the abnormal lipid pattern seen in uncontrolled diabetic state. Lipids should be measured thereafter every year in an adult diabetic. In those with lower risk levels, they may be repeated every 2 years.

The total cholesterol, HDL and triglycerides are to be checked in the fasting state as triglycerides are significantly affected by a meal or alcohol. In diabetic subjects, it is very important to know the LDL as the harmful small dense LDL may be elevated despite a normal total LDL. In most of the laboratories, LDL is calculated by Friedewald formula. However, this is not valid if the serum triglycerides level is elevated in which case, a direct

method of estimating LDL cholesterol can be done in a specialized laboratory.

Treatment Targets

Since the mere presence of diabetes makes one fall into the category of "coronary heart disease risk equivalent", the goal for LDL in persons with diabetes particularly type 2 diabetes is <100 mg/dl, the optimal HDL levels are >40 mg/dl and desirable triglyceride levels are <150 mg/dl.

In patients with clinical cardiovascular disease or very high LDL, pharmacological and behavioral therapy should be started at any level of LDL cholesterol with the goal of achieving LDL <100 mg/dl. In patients without cardiovascular disease, the therapy should start when the LDL level is >130 mg/dl as a goal of <100 mg/dl.

TREATMENT MODALITIES

The cornerstone of the treatment strategies will be:

A) Lifestyle modification

B) Good glycemic control

C) Pharmacotherapy.

A) **Lifestyle modification:** Diet plays an important role and is a necessary foundation of drug treatment. A concerted effect must be made to reduce the intake of saturated fat (<7% of total calories) and cholesterol (<300 mg/day). Other key components are weight reduction and increased physical activity. Stopping of smoking and moderation in alcohol intake is also essential. In addition, a high fiber diet may improve glycemic control and lower plasma lipid concentrations.

B) **Good glycemic control:** Good glycemic control improves the lipid profile especially triglycerides and the LDL cholesterol levels may also decrease modestly. Among oral hypoglycemic agents biguanides and thiazolidinedione drugs especially pioglitazone have been reported to have benefical lipid changes.

C) **Pharmacotherapy:** Four classes of drugs are available: 1) HMG-CoA reductase inhibitors (Statins), 2) bile acid sequestrants (Resins), 3) nicotinic acid and 4) fibric acid derivatives (Fibrates).

The order of priorities for treatment of diabetic dyslipidemia is shown in the Table 1, which are in line with most other national and international guidelines. A brief summary of mechanism of action and dosage of lipid lowering drugs are shown in the Table 2.

LDL CHOLESTEROL

When the lifestyle modification fails, the pharmacological therapy should be started with statin in moderate dose. The response should be checked in 6 weeks time and if goal is not achieved the dose of statin can be increased. If the goal is still not reached, a combination with bile acid sequestrant or nicotinic acid should be tried. Thereafter response to be monitored every 4-6 months.

HDL CHOLESTEROL

Fibrates, nicotinic acid and statins are useful along with lifestyle modifications. Nicotinic acid is to be avoided as it causes insulin resistance and hyperglycemia.

TRIGLYCERIDES

If good glycemic control does not reduce TG levels, fibrates can be added. High dose of atorvastatin may be helpful in reducing TG levels.

CONCLUSION

Dyslipidemia in diabetes continues to be a great clinical challenge and it should be promptly diagnosed and aggressively treated to reduce morbidity and mortality in diabetic subjects.

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