

Diabetic Dyslipidemia

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Cardiovascular disease (CVD) is a significant cause of illness, disability, and death among individuals with diabetes. The macrovascular complications of diabetes— Coronary Heart Disease (CHD), Cerebro Vascular Accidents (CVA), and Peripheral Vascular Disease (PVD)— all being different facets of the same vascular damage – account for more than 70% of all deaths in individuals with diabetes. CVD events are four times more common in individuals with diabetes, occur at a younger age, and have a much greater case fatality rate. This is more so in Indians. Coronary Artery Disease in Indians (CADI) is phenomenon by itself. In fact, people with diabetes and no history of vascular disease have the same risk of having a heart attack or dying of vascular disease as non-diabetic individuals with a prior history of cardio vascular disease. The risk of CVD conferred by diabetes is so great that the National Cholesterol Education Program (NCEP) Adult Treatment Panel III identifies diabetes as a CVD risk equivalent—a condition that requires aggressive care to prevent future vascular events in people with known vascular disease. Despite the fact Dyslipidemia is a significant risk factor for the development of macrovascular complications, awareness and adequate treatment of Dyslipidemia are lacking.

Among the metabolic abnormalities that commonly accompany diabetes are disturbances in the production and clearance of plasma lipoproteins. Moreover, development of Dyslipidemia may be a harbinger of future diabetes. A characteristic pattern, termed Diabetic Dyslipidemia, consists of low high density lipoprotein (HDL), increased triglycerides, and postprandial lipemia. This pattern is most frequently seen in type 2 diabetes and is always a treatable risk factor to prevent CVD.

The Centers for Disease Control and Prevention recently reported that 70–97% of individuals with diabetes have Dyslipidemia. Reports from two academic medical centers document only 35% of patients attending their diabetes clinics were reaching the LDL goal of <100 mg/dl. The management of diabetes, is often referred to as the “ABC” of diabetes. Letter “A” stands for attaining A1c (Hb A1c) of less than 7% or even better 6.5%. “B” stands for maintaining B.P less than 130/80 and the letter “C” reminds patients and providers of the importance of evaluating and treating “cholesterol.” To decrease macrovascular complications in patients with diabetes, equal effort must be applied to controlling lipid levels and blood pressure as well as blood glucose.

Dyslipidemia of Diabetes

The characteristic pattern of lipoproteins in type 2 diabetes includes an increase in triglycerides and a decrease in HDL cholesterol. Concentrations of LDL cholesterol do not differ significantly from concentrations found in non-diabetic individuals but are predominated by the small dense form of LDL. The small dense LDL particles are more intrinsically atherogenic than the normal larger and more buoyant LDL particles. Furthermore, because of their smaller mass, a greater number of LDL particles are contained within the plasma of patients with small dense LDL, further increasing atherogenic risk. This triad of lipid abnormalities, namely increased triglycerides and sLDL and decreased HDL, has been termed “Diabetic Dyslipidemia.”

The presence of Diabetic Dyslipidemia confers a CVD risk estimated to be equivalent to LDL cholesterol concentration of 180–220 mg/dl. In discussing Dyslipidemia, attention has generally focused on the concentration of lipoprotein particles. To understand Dyslipidemia of diabetes, it is important to appreciate the changes in the composition of the lipoproteins that enhance their atherogenicity. The Multiple Risk Factor Intervention Trial (MERFIT) observed that CVD mortality among individuals with diabetes was four times higher than that in nondiabetic individuals with the same concentration of serum cholesterol. Further, diabetic patients in the lowest quintile for serum cholesterol had higher mortality rates than nondiabetic individuals in the highest quintile (figure 1).

Glycosylation, oxidation, and triglyceride enrichment of lipoproteins contribute to the observed increase in the atherogenicity. Glycosylation of LDL increases its half-life, causes it to be the more atherogenic small dense variety, and makes it more likely to be oxidized and taken up by macrophages to form foam cells. Glycosylation of HDL cholesterol shortens its half-life and causes the less protective HDL3 to predominate over the more protective HDL2 form of the lipoprotein. Triglyceride enrichment leads to increased production of the small dense form of LDL cholesterol and to depletion of HDL cholesterol. The ability of HDL to transport cholesterol from peripheral tissues back to the liver may be decreased when HDL is triglyceride enriched. Improvement in blood glucose control as a consequence of lifestyle change or treatment with insulin and an oral antidiabetic agent leads to decreased triglyceride levels, increased HDL levels, decreased glycosylation of lipoproteins, and decreased triglyceride enrichment of lipoproteins.

Goals of Therapy

Treatment of diabetic Dyslipidemia is based on the degree of risk indicated by lipoprotein levels (table 1). The target lipid levels for adults with diabetes are the low-risk category values. Furthermore, it is recommended that all high-risk patients receive drug therapy to manage their Dyslipidemia and that drug therapy, in addition to lifestyle management, be considered even in patients with borderline values. Lipoproteins should be measured at the time of diagnosis of diabetes and after initial blood glucose control is achieved. Because of the frequent changes in glycemic control in patients with diabetes and their effects on lipoprotein levels, a complete lipid profile should be performed every year in all adult patients. If values fall in lower-risk levels, assessment may be repeated every 2 years. More frequent testing may be necessary to assess the response to lipid-lowering therapy and to monitor its progress. In children with diabetes, consideration should be given to measuring lipoproteins after 2 years of age, as suggested by the NCEP Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Initial therapy should begin with medical nutrition therapy (MNT) and physical activity. Weight loss and increased physical activity will lead to decreased triglyceride levels and increased HDL cholesterol levels and also to modest lowering of LDL cholesterol levels. Diabetic patients who are overweight should be given a prescription for MNT and increase physical activity.

American Heart Association recommendations for patients with CVD suggest that the maximal MNT typically reduces LDL cholesterol 15–25 mg/dl. Thus, if the LDL cholesterol exceeds the goal by >25 mg/dl, the physician may decide to institute pharmacological therapy at the same time as behavioral therapy for high-risk patients. In other patients, behavioral interventions may be evaluated at 6-week intervals, with consideration of pharmacological therapy between 3 and 6 months.

Evidence of Treatment Benefit

Randomized controlled clinical trials demonstrate that people with diabetes benefit from cholesterol lowering therapy, with improvements in lipoprotein values and reduced CVD events (table 2). Lipoprotein lowering and improvement in outcomes are equivalent among diabetic and nondiabetic subjects in clinical trials. Results of published trials support the American Diabetes Association's (ADA) recommendations that an LDL cholesterol level <100 mg/dl is the primary target for cholesterol-lowering therapy. The importance of triglyceride lowering is demonstrated in the Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) secondary prevention study, in which there was a 24% reduction in recurrent events using Gemfibrozil. The improved outcomes were achieved without a significant lowering of LDL cholesterol.

Combination therapy

The goal of therapy for diabetic Dyslipidemia is to have all lipoproteins in the desirable range. Because Dyslipidemia generally affects all components of the lipid profile, treatment with a single agent often cannot address the full array of abnormal lipid parameters. Niacin is associated with improvements in all the lipid parameters— LDL cholesterol, HDL cholesterol, triglycerides, and LDL particle size. Although substantial concern previously existed regarding the potential for niacin to raise glucose levels in patients with diabetes, more recent studies suggest that niacin in moderate doses (1–2 g daily) generally has minimal effects on glycemia. Newer formulations of niacin that are generally well tolerated are available, leading to a recommendations in using niacin for managing Dyslipidemia in diabetes. A recent report of atorvastatin plus extended-release niacin demonstrated a 56% reduction in LDL cholesterol, a 69% reduction in triglycerides, a 42% increase in HDL cholesterol, and a 72% reduction in small dense LDL. Statins and fibrates are generally the preferred agents.

Similarly, a recent study of the use of atorvastatin in combination with fenofibrate showed a 46% decrease in LDL cholesterol, a 50% decrease in triglycerides and a 22% increase in HDL cholesterol. It was projected that lipid lowering would result in a decrease from 21.6 to 4.2% in the 10-year probability of a myocardial infarction. Several studies are ongoing to test the safety and efficacy of the use of statins in combination with fibric acid derivatives and nicotinic acid; variably, the package inserts of all statin drugs have either warnings or cautions regarding these combinations. With appropriate caution and patient education regarding the signs and symptoms of myositis, these combinations can generally be used to the patient's advantage.

Patients with average to low LDL levels

The recently reported Heart Protection Study (HPS) included 5,963 individuals with diabetes—the largest number in a cholesterol-lowering trial. The study was designed to determine whether statins (simvastatin) are beneficial to individuals with average to low LDL cholesterol levels. Subjects were divided into three groups by baseline LDL levels: individuals with LDL levels <100 mg/dl, individuals with LDL levels between 100 and 135 mg/dl, and individuals with LDL levels >135 mg/dl. During the first 36 months of the trial, individuals with diabetes had on average a 46 mg/dl decrease in LDL cholesterol and a 35 mg/dl decrease in triglycerides. Overall, therapy resulted in a highly significant 25% reduction in the combination of fatal and nonfatal myocardial infarctions, stroke, and the need for revascularization procedures ($P < 0.001$). The authors encouraged providers to treat patients

with statins based on their risk for CVD events and not on the LDL value alone. In the diabetes setting, this regimen suggests erring on the side of treatment to lower LDL levels, even if the level is about 100 mg/dl. This regimen also suggests giving greater consideration to initiating treatment for lipid disorders with statins and using lifestyle management as adjunctive therapy, opposed to the current approach of using lifestyle management as the primary therapy and only using pharmacological agents when lifestyle management does not result in the patient reaching treatment goals.

Recommendations at a Glance for Patients with Diabetes

A. General recommendations

- Lowering LDL cholesterol to <100 mg/dl is the primary therapy goal for adults.
- Raise HDL cholesterol to >45 mg/dl in men and >55 mg/dl in women.
- Lower triglycerides to <150 mg/dl.

B. Screening

- In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults with low-risk lipid values, repeat lipid assessments every 2 years.
- In children >2 years of age, perform a lipid profile after diagnosis of diabetes and when glucose control has been established. If values are considered low risk and there is no family history, assessments should be repeated every 5 years.

C. Treatment

- MNT focusing on the reduction of saturated fat and cholesterol intake, weight loss, and increased physical activity has been shown to improve the lipid profile in patients with diabetes.
- Patients who do not achieve lipid goals with lifestyle modifications require pharmacological therapy. Preferably in all diabetics pharmacotherapy must be started along with MNT.
- Statins should be used as first-line pharmacological therapy for LDL lowering.
- Niacin extended release preparations are very good choice for low HDL and there is no fear of worsening the glycemic status at the usual doses of less than 2 grams per day
- Therapy with fibrates in patients with high TG and low HDL has been shown to reduce CVD rates and progression of carotid intimal medial progression.
- When prescribing fibrates or niacin in combination therapy with a statin, care is needed to minimize the risk of adverse effects.

The Current Paradigm for management of Diabetes

Diabetes is no longer a mere metabolic disorder pertaining to glucose metabolism alone. We have to now move from mere "*blood sugar control*" to "*blood vessel protection.*" Attaining euglycemia alone is hopelessly inadequate to prevent macro and microvascular complications of DM. Today's goal is to protect all patients from the cardio-vascular complications of diabetes. The emphasis is on "vascular protection" often termed as the VP. Primary prevention of cardiovascular events must be the target

of every physician. What are we to do? How to go about this VP? Every patient of T2DM under our care must receive the following medications irrespective of their B.P. or cholesterol levels.

1. ACEi or ARB must be prescribed – No matter whatever is the B.P.
2. ASA (Aspirin) minimum of 75 mg (women) and 150 mg (in men) must be given to all T2DM
3. Statin (Atorvastatin 10 mg) must be prescribed irrespective of their LDL level
4. Chronic Kidney Disease must be detected and aggressively treated with ACEi or ARB
5. Microalbuminuria and ACR (albumin creatinine ratio) must be evaluated and treated.
6. Early insulin initiation to reduce the burden of hyperglycemia and glycation end products.
7. Metformin must be one of the OHAs unless contraindicated.
8. Pioglitazone must be considered as a part of treatment unless contraindicated.
9. The “ABC” - Hb A1C < 6.5; B.P < 130/80; LDL < 100 mg%, TG < 150%, HDL > 45 (men) > 55 (women) – these goals must be attained as quickly as possible and maintained faithfully.
10. There are no shortcuts in treatment without Medical Nutrition Therapy (MNT) and adequate Physical Activity (PA) in every diabetic patient.

Figure 1
Multiple Risk Factor
Intervention Trial (MRFIT):
Mortality by quintile of total cholesterol

Adapted from Bierman (9).

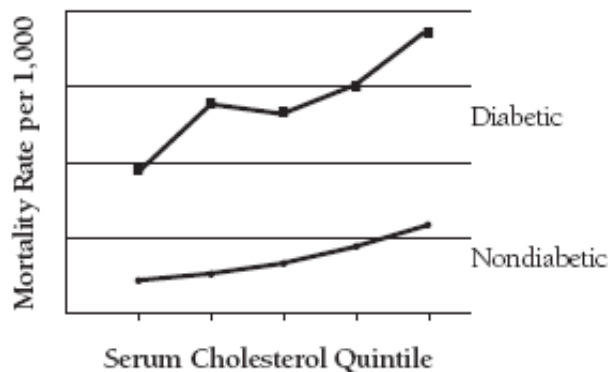


Table 1.

Category of Risk Based on Lipoprotein Levels in Adults With Diabetes

Risk	LDL cholesterol (mg/dl)	HDL cholesterol		Triglycerides (mg/dl)
		Men (mg/dl)	Women (mg/dl)	
High	≥130	<35	<45	≥400
Borderline	100–129	35–45	45–55	150–399
Low	<100	>45	>55	<150

Table 2.

Results of Controlled Clinical Trials of Lipid Lowering in Individuals With Diabetes

Study	LDL cholesterol	HDL cholesterol	Triglycerides	Clinical outcomes
CARE (16)	Decreased 27%	Increased 5%	Decreased 14%	25% risk reduction ($P = 0.05$)
4S (17,18)	Decreased 36%	Increased 8%	Decreased 10%	55% risk reduction ($P = 0.002$) 42% on later analysis ($P = 0.001$)
VA-HIT (19)	No change	Increased 6%	Decreased 31%	24% decrease in CVD death or nonfatal myocardial infarction ($P = 0.05$)
DAIS (20)	Decreased 10%	Increased 6%	Decreased 29%	40% reduction in progression of localized atherosclerotic lesions ($P = 0.02$)
AFCAPS/ TexCAPS (21)	Decreased 25%	Increased 6%	Decreased 15%	33% reduction in CVD events (NS)
HPS (22)	Decreased 29%	Increased 3%	Decreased 14%	26% reduction in first CVD event (final analysis of diabetes incomplete)

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