



Diabetic Dyslipidemia - Clinical Implications

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A B S T R A C T

Cardiovascular disease (CVD) is a significant cause of illness, disability and death among individuals with diabetes. Despite the fact that dyslipidemia is a significant risk factor in the development of macrovascular complications, awareness and proper treatment of dyslipidemia are lacking. The characteristic diabetic dyslipidemia includes – hypertriglyceridemia, low HDL-C, preponderance of small dense LDL-C & post-prandial lipemia. In addition, elevated apolipoprotein B (ApoB) seen in type 2 diabetics is suggested for its use in assessing CVD risk. This atherogenic dyslipoproteinemia is also observed in type 2 diabetic of Indian origin. In our study 82.8% of subjects had low HDL-C (<45mg/dl), 49.13% had triglyceride >150mg/dl and 61.32% had high LDL-C (>100mg/dl). Low HDL-C and high LDL-C are shown to be an independent risk factor amongst CVD group. The normal LDL-C range is 50-70mg/dl for native hunter-gatherers, healthy neonates, free-living primates and other wild mammals (all of whom do not develop atherosclerosis). Randomized trials data suggest atherosclerosis progression and CVD events are minimized, when LDL-C is lowered to < 70mg/dl. Recent NCEP-ATP III guidelines on cholesterol management have included diabetes in the high-risk category. They have recommended LDL-C goal < 100mg/dl in high risk persons, but when risk is very high, an LDL-C goal of < 70mg/dl is a therapeutic option. When LDL lowering drug therapy is employed in high or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least 30 to 40% reduction in LDL-C levels. NCEP-ATP III has emphasized that therapeutic lifestyle changes remain an essential modality in clinical management.

Abbreviations

BMI-Body Mass Index, WHR-Waist Hip Ratio, W-Waist, CVD-Coronary Vascular Disease, HT-Hypertension, CVE-Cerebrovascular Episode, TC-Total Cholesterol, TG-Triglyceride, LDL-C-Low Density Lipoprotein Cholesterol, IDL-C- Intermediate Density Lipoprotein Cholesterol, HDL-C-High Density Lipoprotein Cholesterol, FPG-Fasting Plasma Glucose, Fat U-Unsaturated Fat, Fat S-Saturated Fat, M-Male, F-Female.

INTRODUCTION

Disorders of lipid metabolism are common and prominent in diabetes and are an important risk factor for the high frequency of atheromatous complications in the disease. This is particularly relevant to type 2 diabetes, which currently accounts for at least 95% of all cases worldwide & whose prevalence is rapidly increasing.¹ Epidemiological and clinical studies have repeatedly demonstrated that diabetic individuals have 2-4 times higher risk of developing atherosclerotic cardiovascular disease than non-diabetic individuals.^{2,3} Most patients (65-80%) with type 2

diabetes will die from heart disease⁴⁻⁶ and diabetic women carry a particularly high risk as compared with nondiabetic population.⁷ The International Diabetes Federation (IDF) foresees a rise of epidemic proportions in type 2 diabetes that portends a daunting increase in coronary heart disease.⁸ Solid evidence has confirmed that people with type 2 diabetes have a similar risk of heart attack as people without diabetes who have already had a heart attack.^{9,10} Moreover type 2 diabetes predisposes especially to aggressive CAD that is typically diffuse and affects smaller vessels.¹¹ Coronary heart disease (CHD) in diabetic patient is associated with numerous pathological features, including hypertension, hyperglycemia, abnormal glycation of proteins, dyslipidemia, endothelial dysfunction, microvascular disease, autonomic neuropathy and defects in cardiac structure and function.¹² The term “Diabetic Dyslipidemia” refers to a characteristic pattern of lipid abnormalities consisting of low high-density lipoprotein (HDL), increased triglyceride (TG), preponderance of small dense low-density lipoprotein (LDL) and post-prandial lipemia.¹³ The lipid abnormalities associated with diabetes is better termed

Table 1 : Type 2 Diabetes

Parameters	Male - 1519		Female - 818		p value
	Mean	S.D.	Mean	S.D.	
TC (mg%)	180.96	38.7	191.75	42.7	0.1023
TG (mg%)	178.73	102.3	168.17	90.0	0.0512
HDL-C (mg%)	40.32	6.5	41.79	14.9	0.2156
LDL-C (mg%)	106.25	33.2	116.79	35.7	0.2303
Calories	1845.15	325.2	1666.73	355.3	0.4123
Fat U (gm)	39.33	14.4	40.56	14.6	0.3148
Fat S (gm)	4.07	7.6	2.88	4.7	0.0641
CAD	258 (16.98%)	---	138 (16.87%)	---	0.7152
HT	587(38.64%)	---	404 (49.39%)	---	0.0462
CVE	22 (1.45%)	---	14 (1.71%)	---	0.2221

(a) Mean age, BMI, WHR, waist, FPG, calories intake, fat intake didn't show any significant difference between male & female subjects. (b) No significant difference was seen in mean cholesterol, LDL-C, HDL-C between two groups. Mean TG was higher in males than females (p=0.05). (c) 16.98% male & 16.87% female subjects had documented CAD by resting ECG. Hypertension was more prevalent in females than males (P=0.0462).

Table 2 : Prevalence of Dyslipidemia

Lipid Profile	Male -1519		Female - 818		P value
	Number	%	Number	%	
TC > 200	441	29.03	301	36.8	p=0.0652
TG > 150	770	50.69	389	47.56	p=0.0712
TG > 200	441	29.03	189	23.11	p=0.0526
LDL > 100	862	56.75	539	65.89	p=0.0451
LDL > 130	388	25.54	282	34.47	p=0.0501
HDL < 45	1314	86.5	648	79.22	p=0.0081

(d) Hypertriglyceridemia was more common in male than female (p=0.05), while prevalence of raised LDL-C was higher in females (0.05). Low HDL-C (<45mg/dl) prevalence was more common in male (p=0.0081). If we take HDL-C <55mg/dl for female as abnormal, the relationship will reverse.

as "Dyslipoproteinemia" than "Dyslipidemia" because of changes in both quantity and quality of lipoproteins.¹⁴

LIPOPROTEIN ABNORMALITIES IN DIABETES

Type 1 DM

Untreated type 1 diabetes can cause severe hypertriglyceridemia but lipid levels are nearly normal in non-obese well controlled type 1 diabetics.¹⁵ Hypertriglyceridemia of poorly controlled type 1 DM is due to insulin deficiency causing excessive production of VLDLs by liver & decreased clearance of TG-rich LP (both chylomicrons and VLDLs) because lipoprotein lipase is not activated. Very high TG levels can be often seen together with ketoacidosis. Complications include eruptive xanthomas, acute pancreatitis and lipemia retinalis (a milky appearance of retinal vessels) in funduscopy.

Type 2 DM

Recent developments have recognized the complex nature of diabetic dyslipidemia that is a cluster of potentially atherogenic lipid and lipoprotein abnormalities.¹⁶ Two core components of diabetic dyslipidemia are increased plasma triglycerides and low

concentration of HDL-cholesterol. More recently recognized features are small dense LDL and excessive postprandial lipemia. Their components are not isolated abnormalities but metabolically closely linked to each other.

Factors responsible for diabetic dyslipidemia are:

- (1) Insulin effect on hepatic apoprotein production.
- (2) Regulation of lipoprotein lipase (LpL) activity.
- (3) Action of cholesterol ester transfer protein (CETP).
- (4) Peripheral action of insulin on adipose tissue & skeletal muscles.¹³

Hypertriglyceridemia

The prevalence of raised cholesterol concentration in type 2 diabetes is similar to that in general population. In some cohorts of patient with diabetes, total cholesterol and LDL-cholesterol levels did not associate with cardiovascular risk whereas high triglyceride levels or low HDL-cholesterol concentrations were powerful predictor of CHD events.^{17,18} Tightening of glycemic control may reduce the initial high production rate of large, triglycerides-rich VLDL₁ and increases the direct secretion of small VLDL₂ particles, which have a lower triglyceride : ApoB ratio.¹⁹ Diabetic hypertriglyceridemia results from overproduction of VLDLs and impaired clearance of triglyceride-rich lipoproteins

Table 3 : Impact of LDL-C in CAD subgroup

LDL-C	M (258)	%	Mean TG	Mean HDL	F (138)	%	Mean TG	Mean HDL-C
< 70	34	13.65	162.13	40.04	9	6.52	162.33	43.78
70 - 100	68	27.31	165.51	40.61	36	26.09	133.51	39.77
> 100	147	59.04	168.75	41.02	86	62.32	169.17	43.85
	09 NA*	p = 0.0023			07 NA*	p = 0.0085		

NA* - Subjects with TG > 400mg%, where LDL-C was not calculated

e) More than 60% of CAD subgroup subjects had LDL-C > 100mg%. With increasing LDL-C there was substantial increase in CAD risk (p= 0.0023 in male and p=0.0085 in female). CAD risk is minimum if we keep LDL-C < 70mg% and is maximum if LDL-C > 100 mg%. Type 2 diabetic male with CAD have double the risk of CAD if LDL-C is between 70mg% and 100mg%, while the risk becomes four times if LDL-C is > 100mg% as compared to their counter parts with LDL-C < 70mg%. Type 2 diabetic female with CAD have four times the risk of CAD if LDL-C is between 70mg% & 100mg%, while the risk becomes ten times if LDL-C is > 100mg% as compared to their counter parts with LDL-C < 70mg%. Irrespective of TG or HDL-C, LDL-C is an independent risk factor of CAD in type 2 diabetic population and we should try to keep LDL-C level < 70mg% in cases with pre- existing CAD.

Table 4: Impact of HDL-C in CAD subgroup

		Male		Female					
HDL-C	CAD – no.	%	CAD – no.	%	HDL-C	Male -TG	Female -TG		
< 35	47	18.15	24	17.39		< 150	> 150	< 150	> 150
35 - 45	172	66.41	76	55.07	< 45	109	110	55	48
45 - 55	26	10.04	32	23.19	45 - 55	10	16	12	19
> 55	14	5.41	6	4.35	> 55	4	10	2	4

f) 84.6% of male and 72.5% of female had HDL-C < 45mg%, while 95.65% of female had HDL-C < 55mg% in CAD subgroup. Irrespective of level of TG, low HDL is independent risk factor for CAD in type 2 diabetics. With increasing HDL-C, if TG is kept below 150mg%, it may offer CAD protection in both sexes.

g) In CAD subgroup, triglyceride didn't show any statistically significant co-relation.

(TRL) due to decreased LPL activity.^{20,21} One major consequence of LPL action is to convert VLDL₁ to VLDL₂, which explains the change in the triglyceride : ApoB ratio. The prolonged residence time of the triglyceride-rich lipoproteins in the circulation leads to increased exchange of their triglyceride for cholesteryl esters in HDLs (as well as in LDLs) by the cholesteryl ester transfer protein [CETP]. These neutral lipid exchanges cause decreases in both HDL- and LDL-cholesterol concentrations, leading to relatively cholesteryl ester-depleted LDL and HDL particles, which also become smaller following hydrolysis of their unusually rich triglyceride core by the hepatic lipase. This increased bidirectional triglyceride-cholesteryl ester exchange in hypertriglyceridaemic patients with type 2 diabetes explains why fasting triglyceride concentration is an accurate predictor of LDL size.²² Triglyceride-enriched HDLs and LDLs are produced and are then hydrolysed by hepatic lipase to produce small dense LDL and HDL particles; the latter are rapidly cleared from the circulation, leading to lower serum HDL-cholesterol concentrations. In diabetes, the plasma triglyceride concentration is negatively correlated with that of large HDL₂ and positively correlated with the level of small HDL₃, an indication of the impact of triglyceride-enriched lipoproteins on HDL concentration and composition.^{23,24} This change is also relevant to cardiovascular risk in diabetes, as HDL₂ which is relatively depleted, has the greater antiatherogenic effect. These intricate metabolic interrelationships complicate the assessment of triglyceride, HDL and LDL concentration and of LDL and HDL size as independent predictors of CHD risk in type 2 diabetes. For instance, a low HDL-cholesterol concentration is a

heterogeneous phenotype,^{25,26} but in patients with type 2 diabetes, is most often a component of the metabolic syndrome that is typically accompanied by moderate hypertriglyceridaemia.²⁷ The low HDL-cholesterol in patients with the metabolic syndrome can substantially raise the total cholesterol/HDL-cholesterol ratio, which was found to be the best lipid index for predicting cardiovascular events in prospective studies such as the Framingham Heart Study and the Quebec Cardiovascular Study.^{28,29}

Apo-B concentration

In addition to low HDL-cholesterol and hypertriglyceridaemia, an elevated ApoB concentration is another common feature of the dyslipidaemia of type 2 diabetes. Indeed, an increase in ApoB levels may predict CHD events better than the LDL-cholesterol level.³⁰⁻³² ApoB is required for the hepatic secretion of VLDL, and each VLDL particle contains one ApoB molecule; ApoB remains associated with the particle until its clearance from the circulation as IDL or LDL. Thus, the ApoB level reflects the total concentration of atherogenic particles (VLDLs, IDLs and LDLs), of which LDL accounts for ≈95% of circulating ApoB.³³ ApoB is susceptible to glycation in diabetes, which impairs its interaction with the hepatic LDL receptor (B/E)³⁴ and slows the clearance of LDL; accordingly, the plasma half-life of the particle is increased. Elevated ApoB are found in almost half of normocholesterolaemic patients with type 2 diabetes and are frequently associated with low HDL-cholesterol levels and hypertriglyceridaemia.³⁵ Given this high incidence among

Table 5 : Relation of HDL-C with exercise

	Males - Exercise				Females- Exercise			
	Yes	%	No	%	Yes	%	No	%
Total	650	42.79	869	57.21	292	35.7	526	64.3
HDL-C < 45	547	84.15	767	88.26	223	76.36	424	80.61
HDL-C > 45	103	15.85	102	11.74	69	23.64	102	19.39
	p < 0.005				p < 0.005			

Impact of Exercise on Lipids: 42.8 % of male and 35.7% of female subject were practicing regular physical exercise [walk>20min /day, 5days/week]. HDL-C was higher in both groups, who were doing exercise [male-P<0.005, female P<0.005] while TG and LDL-C didn't show any statistically significant co-relation with exercise.

Table 6 : ATP III LDL-C Goals and Cut Points for Therapeutic Lifestyle change (TLC) and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence⁸³

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy**
High risk : CHD* or CHD risk equivalent † <100 mg/dL (10year risk > 20%)	≥ 100 mg/dL # (optional goal: <70mg/dL)	≥ 100 mg/dl ††	(<100mg/dL: consider drug options)**
Moderately high risk : 2 + risk factors† (10-year risk 10% to 20%)§§	<130 mg/dL ¶	≥ 130 mg/dL#	≥ 130 mg/dL (100-129mg/dL;consider drug options)++
Moderate risk : 2 + risk factors** (10 year <130 mg/dL risk < 10%) §§	≥ 130 mg/dL	≥ 160 mg/dL	
Lower risk 0-1 risk factors §	< 160 mg/dL	≥ 160 mg/dL	≥ 190 mg/dL (160-189mg%:LDL-lowering drug optional)

* CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

† CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2 + risk factors with 10 year risk for hard CHD > 20%.

** Risk factors include cigarette smoking, hypertension (BP ≥ 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40mg/dL), family history of premature CHD (CHD in male first-degree relative <55years of age; CHD in female first-degree relative < 65 years of age), and age (men ≥ 45years; women ≥ 55years).

§§ Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

§ Almost all people with zero or one risk factor have a 10 year risk < 10%, and 10-year risk assessment in people with zero or one risk factor is thus not necessary.

|| Very high risk favors the optional LDL-C goal of <70mg/dL, and in patients with high TG, non-HDL-C<100 mg/dL.

¶ Optional LDL-C goal <100mg/dL.

Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g. obesity, physical inactivity, elevated TG, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

** When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

++ If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high TG or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

++ For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100mg% is a therapeutic option on the basis of available clinical trial results.

patients with type 2 diabetes, it has been suggested that ApoB levels should be used systematically to assess cardiovascular risk in this population.³⁶ High proportion(60%) of diabetic patients with vascular complications have elevated ApoB levels and half of these patients also have low HDL-cholesterol levels.³⁵ Thus the measurement of ApoB may help to identify a group of subjects who should be treated actively, especially those with moderate hypertriglyceridaemia. However, prospective studies are necessary to justify this proposal and to identify the cut-

off values above which an elevated ApoB concentration reliably predicts clinical risk.

LDL-Density

LDL distribution is tilted towards smaller and denser LDL-3 particles (LDL-Phenotype), which have greater atherogenic potential.³⁷ Small LDL particles have reduced affinity for LDL receptor, prolonging their residual time in the plasma and thus increasing their susceptibility to oxidation.

Table 7 : Recommendations for Modifications to Footnote the ATP III Treatment Algorithm for LDL-C on the basis of available clinical trial evidences.

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management, TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
- In high-risk person, the recommended LDL-C goal is <100 mg/dL.
 - An LDL-C goal of <70 mg/dL is a therapeutic option, especially for patients at very high risk.
 - If LDL-C is \geq 100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
 - If baseline LDL-C is <100mg/dl, institution of an LDL-lowering drug to achieve an LDL-C level <70mg/dL is a therapeutic option.
 - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are \geq 200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- For moderately high-risk persons (2 + risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; an LDL-C goal <100 mg/dL is a therapeutic option. When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option. Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g. obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cut-points of therapy.

Small dense LDL particles are observed at even marginally elevated triglyceride levels³⁸ and the presence of hypertriglyceridaemia in obese patients with type 2 diabetes is a reliable predictor of the presence of small dense LDL particles. Approximately 25% of patients with type 2 diabetes but without cardiovascular disease show the small dense LDL phenotype.^{39,40} The LDL particles from men with type 2 diabetes have also been shown to be more potent at inhibiting endothelium-dependent relaxation than LDLs from normal controls.⁴¹ With improved metabolic control, the concentration of small dense LDL falls and the LDL density distribution shifts away from pattern B.⁴² Furthermore, because of the strong influence of hypertriglyceridaemia on LDL size, any treatment that significantly lowers TG levels is likely to have an impact on LDL size & thus ultimately on related CHD risk.

Postprandial Lipemia

Postprandial lipemia (fat intolerance) is a distinct component of diabetic dyslipidemia.^{16,43-46} Several studies have shown that the response of plasma triglycerides to a standard fat load is much greater in type 2 diabetic subjects than in non-diabetic subjects matched for age, sex and BMI.^{16,43-46} Importantly, the peak concentration of plasma triglycerides are achieved at 4 to 6 hrs. after the fat load. Thus the time course of TG response is markedly different from that observed after a glucose load where glucose concentrations are back at the baseline level at 3 to 4 hrs. The triglyceride profile shows that after breakfast, the triglyceride concentrations gradually increased after consecutive meals and the peak concentration was achieved between dinner and bedtime. In this context it is important that the fasting triglycerides represented the nadir of the 24-h triglyceride profile. A persuasive conclusion is that type 2 diabetic patients are exposed to high triglyceride concentration throughout most of the 24h a day, which is a key determinant of both LDL size and HDL-cholesterol.

Is Postprandial Lipidemia a Hazard ?

The important implication is that postprandial lipemia has severe adverse consequences at the level of the arterial wall. A number of studies have shown that postprandial lipemia is linked with the

endothelial dysfunction and generation of oxidative stress in type 2 diabetic patients.⁴⁷⁻⁵⁰ Post-meal metabolic excursions comprise a cluster of potentially highly atherogenic perturbations that could be more important in terms of damaging the arterial wall than those due to hyperglycaemia.⁵¹ In addition, lipoproteins and remnants can also interact with coagulation factors.^{52,53} In this context, a persuasive hypothesis is that a fatty meal is a trigger for acute coronary syndrome.⁵⁴ Therefore, it is not surprising that the postprandial state is in the spotlight of current research.

Lipoprotein (a) [Lp(a)]

This is an LDL particle, which has an additional apoprotein, designated as Apo(a), attached covalently to the Apo B100. Apo (a), a large glycoprotein, shares a high degree of sequence homology with plasminogen, is produced by liver. The physiologic role of lipoprotein(a) is not well understood. However, it's elevation (>30mg/dl) is associated with an increased risk of atherosclerosis.^{55,56} Studies have shown higher levels,⁵⁷ no difference⁵⁸ and even lower levels⁵⁹ in type 2 diabetics. The consensus appears to be that the diabetic state does not have any impact on Lp(a) concentration⁶⁰ though diabetic patients with CHD found to have higher Lp(a) levels than diabetic patients without CHD.⁶¹ Study from South India says that in diabetic population Lp(a) is an independent risk factor for CHD though the level is not increased.⁶² Lp(a) concentrations found to be higher in those with CAD and proteinuria, while no association was found with retinopathy or PVD in South Indian type 2 diabetics.⁶³

PREVALENCE OF DIABETIC DYSLIPIDEMIA- INDIAN SCENES

In Indian, distinctive lipid profile include hypertriglyceridemia, low HDL-C, high proportion of small dense LDL cholesterol (dLDL), increased apolipoprotein B-100, decreased apolipoprotein A, and increased lipoprotein(a) [Lp(a)].⁶⁴⁻⁷⁰ Indians are found to have lower HDL-C and higher Lp(a) than Malays and Chinese.⁷¹ The combination lipid abnormalities in Indians mentioned above has been termed as "atherogenic" and is known to be initiated

Table 8 : Order of Priorities for Treatment of Diabetic Dyslipidemia in Adults⁸⁹

1. **LDL cholesterol lowering*:**
 - First choice: HMG CoA reductase inhibitor (statin).
 - Second choice: Bile acid binding resin or fenofibrate
2. HDL cholesterol raising:
 - Behavioral interventions such as weight loss, increased physical activity, and smoking cessation may be useful
 - Nicotinic acid, which on occasion will raise glucose significantly, or fibrates (gemfibrozil, fenofibrate)
3. Triglyceride lowering:
 - Glycemic control is the first priority
 - Fibric acid derivative (gemfibrozil, fenofibrate)
 - High doses of statins are moderately effective in hypertriglyceridemic subjects with high LDL cholesterol.
4. **Combined hyperlipidemia:**
 - First choice : improved glycemic control plus statin
 - Second choice : Improved glycemic control + statin + fibric acid derivative # (gemfibrozil, fenofibrate)
 - Third choice : Improved glycemic control +resin + fibrates (gemfibrozil, fenofibrate); Improved glycemic control + statin + nicotinic acid (monitor glycemic control)

* The decision to treat high LDL levels before elevated triglycerides was based on clinical trial data indicating safety as well as efficacy of the available agents.

The combination of statins with nicotinic acid and especially with gemfibrozil or fenofibrate may carry an increased risk of myositis.

and perpetuated by insulin resistance. Studies in neonates suggest that the tendency of Indians towards adiposity and insulin resistance originates in utero.⁷² The exaggerated risk of insulin resistance syndrome in Indians at a relatively lower body mass index (BMI) may be due to excess total fat and a tendency toward central adiposity. A recent study in the United States confirmed that Indians have a high percentage body fat, higher central visceral fat and higher posterior subcutaneous abdominal fat than Caucasians and this was associated with higher insulin resistance in Indians.⁷³ In South Asians, insulin resistance is associated with high rates of coronary artery disease, raised plasma triglyceride, low HDL cholesterol (HDL-C), alterations in LDL subfraction pattern, and central obesity.⁷⁴ An Indian study has shown 76% of type 2 diabetics with raised LDL-C [$> 100\text{mg}\%$], low HDL-C [$< 35\text{mg}\%$] seen in 58% and hypertriglyceridemia [TG $> 100\text{mg}\%$] in 22% cases.⁷⁵

OUR EXPERIENCE

In continuation of our previously published data⁷⁶⁻⁷⁸ 2337 type 2 diabetic subjects between 30-70yrs age with 1519 males (65%) and 818 (35%) females were selected. We studied the lipid profile and have co-related it with age, sex, body mass index (BMI), waist-hip ratio (WHR), waist (W), glycemic status, coronary heart disease (CHD) and hypertension (HT).

GOALS OF THERAPY

Optimal Low-Density Lipoprotein

The normal LDL-C range is 50-70mg/dl for native hunter-gatherers, healthy neonates, free-living primates and other wild mammals (all of whom do not develop atherosclerosis). Randomized trials data suggest atherosclerosis progression and CVD events are minimized, when LDL-C is lowered to $< 70\text{mg}/\text{dl}$.⁷⁹ According to the National Cholesterol Education Program Adult Treatment Panel III [NCEP-ATP III] the target LDL level for patient with established CHD or CHD equivalent (such as diabetes peripheral or cerebral vascular disease, or predicted 10 year CHD risk of $> 20\%$) is $< 100\text{mg}/\text{dl}$.⁸⁰ The

European guidelines set the LDL target at $< 115\text{mg}/\text{dl}$,⁸¹ while accumulating data from the physiologically normal LDL level and the thresholds for atherosclerosis development and CHD events are approx. 50-70mg%.⁷⁹

Recent NCEP - ATP III Guidelines:⁸²

Since the publication of ATP III, five major clinical trials with statin therapy and clinical end-points have been published. These include the Heart Protection Study (HPS),⁸³ the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER),⁸⁴ Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial-Lipid-Lowering Trial (ALLHAT-LLT),⁸⁵ Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA),⁸⁶ and the Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial.⁸⁷ On the basis of results of these trials ATP III identified diabetes as a high-risk condition.

Diabetes plus CVD - In HPS patients who had both diabetes and CVD were at very high risk for future CAD event.⁸⁸ In terms of absolute risk reduction, this category of patient obtained the greatest benefit from statin therapy. Therefore, patient with the combination of diabetes and CVD deserve intensive lipid-lowering therapy. On the basis of HPS, the presence of this combination appears to support initiation of statin therapy regardless of baseline LDL-C levels. For patients with diabetes plus CVD, it is a reasonable to attempt to achieve a very low LDL-C level (e.g. $< 70\text{mg}/\text{dl}$).

Diabetes without CVD

ATP III indicated that most patients with diabetes are at high risk even in the absence of established CHD. HPS data found both a high risk in this group and benefit from LDL-lowering therapy, supporting the LDL-C goal of $< 100\text{mg}/\text{dl}$. In those diabetic patients without CVD who had an LDL-C at baseline of $< 116\text{mg}/\text{dl}$, risk reduction accompanying statin therapy was only marginally significant for first coronary event. Thus, whether to start an LDL-lowering drug when LDL-C is $< 100\text{mg}/\text{dl}$ in

this category of patient must be left to clinical judgment. For the category of moderately high risk (10 year risk 10% to 20%), ATP III favored institution of LDL-lowering drugs with dietary therapy when LDL-C levels are $\geq 130\text{mg/dL}$. Thus, if a patient with diabetes is at lower risk, an LDL-lowering drug might not be started if the LDL-C level is $< 130\text{mg/dL}$.

Recommendations at a glance for patients with diabetes:⁸⁹

General recommendations

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

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.

Treatment

- Medical Nutritional Therapy (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.
- Patients who do not achieve lipid goals with lifestyle modifications require pharmacological therapy.
- Statins should be used as first-line therapy for LDL lowering.
- Therapy with fibrates in patients with low HDL has been shown to reduce CVD rates and progression of carotid intimal medial progression.

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