Clinical Forum

Dyslipidaemia in type 2 diabetes mellitus

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Introduction

Macrovascular diseases like coronary heart disease (CHD), cerebrovascular accidents (CVA) and peripheral vascular disease (PVD) are the leading causes of mortality and morbidity in type 2 diabetes mellitus (DM). Type 2 DM is associated with two-to-four fold excess risk of CHD, higher case fatality rate and sudden cardiac deaths. There is also a five-fold increase in risk of fatal stroke and a significantly increased risk of atherosclerosis-induced gangrene of lower limbs as compared to non-diabetic individuals.[1-5] The increased atherosclerosis risk in DM is attributed to the high prevalence of several predisposing factors like obesity, hypertension, insulin resistance and dyslipidaemia in these patients. Although the degree of glycaemia in diabetic patients is strongly related to the risk of microvascular disease (retino-pathy, nephropathy), the relationship of glycaemia with macrovascular disease in type 2 DM is less certain.[6] There is enough evidence in literature[7-11] to support the beneficial effect of lowering of serum lipids in retarding macrovascular disease. It is important to realise that hyperlipidaemia and the resultant macrovascular disease can develop even in the 'prediabetic phase' of type 2 DM.[12] Hence, early detection and correction of dyslipidaemic state is essential in the management of diabetic patients.

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Lipid abnormalities

The most common pattern of dyslipidaemia in type 2 DM is elevated triglyceride (TG), decreased high density lipoprotein (HDL) and normal to slightly higher low density lipoprotein (LDL) levels.[13] The cause of hypertrigly-ceridaemia is over-production and delayed catabolism of very low density lipoprotein (VLDL) TG and decreased lipoprotein lipase activity. Furthermore, TG enrichment of VLDL may lead to increased uptake of VLDL into arterial wall. Decreased HDL cholesterol levels are due to increased catabolism of HDL cholesterol because of increased hepatic TG lipase activity and decreased production of HDL cholesterol secondary to impaired catabolism of VLDL.[14]

In type 2 diabetic patients, even if absolute concentration of LDL cholesterol is not significantly increased qualitative changes in LDL cholesterol

occur with preponderance of smaller, denser, oxidised and desialiated LDL cholesterol particles which possibly increases atherogenicity.[13,15] The oxidised portion of the LDL molecule becomes antigenic and stimulates production of antibodies both within the vascular wall and circulation. It also damages endothelial cells and impairs production of nitric oxide (endothelial relaxing factor). It attracts monocytes to the vascular wall and mediates their migration into subendothelial space with conversion into macrophages which avidly uptake cholesterol to produce foam cells. It has also been shown to stimulate growth factors, produce adhesion molecules attracting circulating elements into the vessel wall and finally incites the production of cytokines or inflammatory molecules.[16]

Diagnosis of dyslipidaemia

The American Diabetes Association (ADA, 1998)[17] guidelines categorise the CHD risk based on various lipid levels as higher, borderline and lower risk (Table 1). Hence, for type 2 diabetic patients the optimal level for LDL cholesterol is <2.6 mmol/L (100 mg/dL), HDL cholesterol is > 1.15 mmol/L (45 mg/dL) and TG is <2.30 mmol/L (200 mg/dL).

Table1: Category of CHD risk based on Lipoprotein levels in type 2 diabetics

Risk	LDL Cholesterol	HDL Cholesterol	TG
Higher	≥ 130	<35	≥400
Borderline	100-129	35-45	200-399
Lower	<100	>45	<200

Data are given in milligrams per deciliter

A complete lipid profile should be obtained in all patients with type 2 diabetes. The elderly should not be denied the benefit of lipid optimising therapy solely on the basis of advanced age.[18] In patients with acute myocardial infarction lipid profile should be done at the time of admission or no later than in the first 24 hours; otherwise a minimum 4-week waiting period is required after acute myocardial infarction to allow the lipid fractions to stabilise. [19]

Benefits of correction of dyslipidaemia

The benefits of serum lipid lowering include reduction of total mortality and morbidity in diabetic patients. There is reduction of CHD events such as nonfatal myocardial infarction, unstable angina, sudden cardiac deaths, revascularisation procedures (CABF/PTCA), and number and duration of hospitalisation. Incidence of transient ischaemic attacks/cerebral stroke is also reduced.[7,8]

Recent landmark trials like Scandinavian Simvastatin Survival Study (4S)[7] and Cholesterol and Recurrent Events (CARE)[8] with statins have shown that by lowering LDL cholesterol by 30-40% a significant reduction in CHD incidence by 55% (p= 0.002) and 25% (p=0.05) respectively can be achieved. Hence, primary emphasis should be placed on LDL lowering, but interventions to lower triglyceride levels and raise HDL cholesterol are also beneficial.[2,20] However, elevated serum triglyceride levels are also associated with other risk factors like obesity, hypertension and insulin resistance and lowering TG levels alone may not change the actual risk of CHD.[17]

Therapy

Aggressive lipid lowering should be started as soon as the diagnosis of diabetic dyslipidaemia is established. The treatment goal is to achieve the target level of LDL cholesterol <100 mg/dL, TG <200 mg/dL and HDL cholesterol >45 mg/dl.[17]

(a) Behavioural modification- Diet, Exercise

Diet

Reduction in caloric intake (particularly those from saturated fatty acids) to approximately 500 Kcal/day less than the amount required for maintenance of body weight can result in losses of 1-2 kg per month. A total loss of 5-9 kg weight decreases hyperglycaemia, dyslipidaemia and hypertension.[21] In obese patients serum TG levels are generally very sensitive to weight loss, decreasing early and staying at reduced levels as long as weight loss is maintained. A decrease in LDL cholesterol and increase in HDL cholesterol level is seen by 1 to 2 months.[22]

Out of the total daily calories, 50-60% should be derived from complex carbohydrates, 10-20% from proteins and <30% from fat. The polyunsaturated fatty acids (PUFA) and monosaturated fatty acids (MUFA) should form 10% and 10-15% of calorie source respectively. Saturated fatty acids (SAFA) which are atherogenic and thrombogenic should make up for <10% of total calories if LDL cholesterol levels are normal but if they are raised it should be limited to less than 7%.[21,23] The SAFA intake can be lowered by avoiding butter, ghee, replacing skimmed milk for full fat milk, lessening the use of dairy fat (cakes, pastries etc). No more than 230 g (8 oz) of lean meat and shell fish should be consumed daily. Liberal use of coconut oil and palm oil should be discouraged. Similarly, vanaspati, margarines, fried chicken and bakery products rich in trans-saturated fatty acids (most dangerous) should be totally discarded from a diabetic diet. Increased consumption of MUFA such as groundnut oil, olive oil, sesame oil and high oleic varieties of safflower or sunflower oils is advisable.[24]

There is no single vegetable oil which provides an ideal proportion of SAFA, PUFA and MUFA. It is better to use either a mixture of oils or to change the oil from time to time. Sunflower oil and groundnut oil (or olive oil), mixed in equal proportions provide about 20% of fat calories from SAFA and nearly 40% each from PUFA and MUFA. This is one of the most acceptable mixtures.

The supplementation of ω-3 PUFA which is antithrombogenic is best accomplished by weekly or biweekly use of fatty fish such as salmon, mackerel, farm raised catfish and fiber rich green leafy vegetables. Daily consumption of five or more servings of fruits and vegetables would provide most of necessary antioxidants.[24]

Alcohol should be best limited to two standard drinks per day for men and 1 per day for women as it worsens hypertriglyceridaemia, provides useless calories, worsens insulin resistance, raises noncardioprotective HDL-3 and may precipitate pancreatitis. Diabetics with raised TG should totally avoid alcohol.[21]

Exercise

Aerobic exercise at 50-70% of an individuals maximum O_2 uptake for minimum 20-45 minutes per day for at least 3 days a week should be done. Exercise should be appropriate to an individuals general physical condition and life style.[25] Alternatively, brisk walking, jogging or swimming for 30 minutes on most days of the week are recommended for diabetic patients.[26] Regular exercise has consistently been shown to be effective in reducing TG rich VLDL cholesterol levels. However, effect on LDL cholesterol has not been consistently documented and most studies have failed to demonstrate a significant improvement in levels of HDL cholesterol.[17]

The ADA (1998) suggests that behavioural interventions may be evaluated at 6 weeks intervals with consideration of pharmacological therapy between 3 and 6 months. However, in those patients with a prior myocardial infarction, CVA, PVD and/ or other CHD risk factors, or those who have already made all of the life style changes the pharmacological therapy may be initiated earlier with behavioral modifications simultaneously.[17] The maximal behavioural interventions typically reduce LDL cholesterol 15-25 mg/dl only; thus ,if the goal exceeds by > 25 mg/dl, the physician may decide to institute pharmacological therapy earlier.[27]

(b) Glycaemic control

Optimisation of glycaemic control should be the first step in the approach to elevated triglyceride and LDL cholesterol, as well as to low HDL cholesterol levels. It improves diabetic dyslipidaemia (especially hypertrigly-ceridaemia) irrespective of the mode of treatment i.e. sulfonylurea, metformin, insulin, acarbose, or troglitazone. The magnitude of triglyceride lowering is directly related to the degree of glycaemic control achieved. However, the effect of improved glycaemic control on HDL cholesterol is more variable and LDL cholesterol levels are reduced only modestly.[28]

(c) Lipid lowering drugs

The order of priorities for treatment of diabetic dyslipidaemia is summarised in Table 2. The first priority is lowering LDL cholesterol with statins (HMG Co-A reductase inhibitors) or as a second choice with resins or fenofibrate. In uncontrolled diabetic patients with high LDL cholesterol one should simultaneously initiate behavioural modification, glucose lowering and statin therapy.[17]

The recommended starting daily dose of lovastatin is 10-20 mg, pravastatin 10mg, simvastatin 5-10mg, fluvastatin

Table 2: Order of priorities for treatment of diabetic dyslipidaemia

I	LDL cholesterol lowering
	First choice - Statins
	Second choice - Resins, fibric acid derivative (fenofibrate)
II	HDL Cholesterol raising
	Weight loss, exercise and cessation of smoking may be useful
	Difficult except with nicotinic acid, which is relatively contraindicated
III	Triglyceride lowering
	Glycaemic control first priority
	Fibric acid derivative
	Statins are moderately effective at high dose in hyperglyceridaemic subjects who also have high LDL cholesterol
IV	Combined hyperlipidaemia
	First choice - Improved glycaemic control plus high dose statin
	Second choice- Improved glycaemic control plus statin plus fibric acid deivative
	Third choice- Improved glycaemic control plus resin plus fibric acid reivative
	Improved glycaemic control plus statin plus nicotinic acid

20 mg and atorvastatin 10 mg. A single dose in the evening is given since cholesterol biosynthesis is greatest during night and early morning hours.[29] If needed the dose may be doubled and the patient reassessed after another 4-8 weeks. However, recently, higher starting daily doses have been suggested for pravastatin (40 mg) and simavastatin (20 mg).[30] Generally the majority of LDL cholesterol lowering effect will be seen with the starting dose, doubling of the dose will reduce LDL cholesterol by another 7%.[31] Dosage of statins may be titrated to the maximum recommended dose or another LDL cholesterol lowering drug like niacin or resin may be added for an additive effect. The maximum recommended dosage per day for lovastatin, fluvastatin and atorvastatin is 80 mg, while for pravastatin and simvastatin is 40 mg. Table 3 shows dose-related LDL cholesterol lowering with various lipid lowering drugs.

The patients on statin therapy should be advised that nausea, headache, constipation and epigastric discomfort are mild and self limiting. Baseline values of SGOT and SGPT should be obtained and rechecked after 4-8 weeks. If enzyme levels are normal, it is

Table 3: Dose related LDL cholesterol lowering with various lipid lowering drugs.

Drug	Daily dosage	LDL cholesterol lowering
1. Niacin (crystalline)	1000mg	-6%
	1500mg	-13%
	2000mg	-16%
	3000mg	-22%
2. Bile acid resins (colestipol)	5 g	-15%
	10g	-23%
	15g	-27%
3. Fibric acid derivative		
a. Gemfibrozil	1200mg	Variable
b. Fenofibrate	200mg	-25%
4. Statins		
a. Lovastatin	20mg	-24%
	40mg	-34%
	80mg	-40%
b. Pravastatin	10mg	-22%
	20mg	-32%
	40mg	-34%
c. Simvastatin	5mg	-24%
	10mg	-33%
	20mg	-33%
	40mg	-40%
d. Fluvastatin	20mg	-18%
	40mg	-22%
	80mg	-28%
e. Atorvastatin	10mg	-41%
	20mg	-43%
	40mg	-50%
	80mg	-61%

appropriate to recheck these levels after one year. If they are more than 3 times the baseline values the dose of statins is reduced or therapy is discontinued. No permanent liver damage has been reported as a result of statin therapy. Once SGOT, SGPT levels have returned to normal levels, therapy with statins may be reinitiated at low doses with careful monitoring of serum enzymes.[2] If patient reports symptoms of muscle pain, aching or weakness the serum creatine phospokinase (CK) should be done and if it is more than 10 times the upper limit of normal, the therapy should be stopped. Rarely rhabdomyolysis and acute renal failure may complicate statin therapy.[29] Statins should be temporarily withdrawn in conditions predisposing to rhabdomyolysis such as severe infections, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorder, uncontrolled seizures and should not be coadministered with erythromycin and ketoconazole.[32] Low doses should be initiated in patients with severe renal or hepatic failure or on cyclosporine.[29] Myopathy is rapidly reversible if diagnosed early and treated with volume repletion and discontinuation of statin therapy which may be restarted at a reduced dose later on. Routine and periodic CK measurement usually does not have any benefit in predicting myopathy.[32]

Table 4: Lipid lowering drugs used in diabetic dyslipidaemia

Drugs	Daily dose	Side effects	Comments	Change(%)
Niacin	$\leq$ 2g	Flushing, itching, dyspepsia, rash; activates peptic ulcer, inflammatory bowel disease, bronchial asthma	Disturbs glycaemic control hence strict monitoring. May be used in combined dyslipidaemia	LDL- 20 to –30 HDL+10 to+35 TG-30 to -50
Resins				
Cholestyramine Colestipol	8-12 g 10-15g Use with juice, milk curd etc	Constipation, bloating, flatulence, impaired absorption of warfarin, digoxin, thyroxin, hence taken 1 hour before or 4 hours after resins.	Not first line. Used to lower LDL-c only when TG controlled with fibrates	LDL –15 to –30 HDL 0 to +5 TG 0 to +15*
Fibrates				
Clofibrate Gemfibrozil Bezafibrate Fenofibrate	2 gm 1200mg 400mg 200mg	Dyspepsia, headache itching, myopathy, gallstones. Gemfibrozil may have carcinogenic potential	First choice for isolated raised TG; may increase LDL-c hence statins should be added if LDL-c+ TG raised	LDL-5 to -25• HDL +10 to +25 TG –20 to -50
Statins				
Lovastatin Pravastatin Simvastatin Fluvastatin Atorvastatin	20-80mg 10-40mg 10-40mg 20-80mg 10-80mg	Nausea, Vomiting dyspepsia Headache, raised liver enzymes, Myositis, rhabdomyolysis & acute renal failure are rare	First line agents for lowering LDL-c safer, no unfavourable effect on glycaemic status	LDL–30 to –40 HDL +5 to +15 TG- 20 to -25

* TG levels may increase by $\geq$ 100% in patients with pre-existing hypertriglyceridaemia

• Fibrate therapy alone may worsen LDL cholesterol levels in patients with hypertriglyceridaemia

The second priority is to raise HDL cholesterol. The behavioural modification like weight loss, exercise and cessation of smoking are of limited efficacy. Nicotinic acid is beneficial in raising HDL cholesterol but as it worsens glycaemic control, it is relatively contraindicated in patients with diabetes.[17]

The third priority is to lower triglycerides. The initial therapy for hypertriglyceridaemia is behavioural modification with weight loss, increased physical activity, low fat, low carbohydrate diet, cessation of alchohol consumption and good glycaemic control. In mild hypertriglyceridaemia (serum TG level 200-400 mg/dl) the decision to start pharmacological therapy is dependent upon clinicians judgement. But if serum triglyceride level is above 400 mg/dl, strong consideration should be given to pharmacological treatment using fibric acid derivatives like gemfibrozil (600 mg twice daily), bezafibrate (400 mg once daily) or fenofibrate (200 mg once daily). Fenofibrate has better LDL cholesterol lowering efficacy than other fibrates.[17]

For combined dyslipidaemia higher dosage of statins are suggested as first choice. Atorvastatin (40 mg-80 mg per day) can be used for high serum TG and LDL cholesterol levels with reduction of LDL cholesterol up to 52% and TG up to 33%[33] while simvastatin (80 mg-160 mg per day) can reduce LDL cholesterol upto 53% and TG upto 33%[34] but has not yet been approved for clinical use in such higher dosage. Gemfibrozil should not be initiated alone in diabetic patients who have combined TG and LDL cholesterol dyslipidaemia as it adversely affects LDL cholesterol levels. Instead statins should be added or fenofibrate may be used. The details of various lipid lowering drugs is summarised in Table 4.

Combined treatment with two or more lipid lowering drugs is reserved for patients who do not respond adequately to monotherapy or to reduce the risk of adverse effects of maximal dosage of single drug. Combination treatment with statins and fibrates lowers TG by 16% in addition to LDL cholesterol lowering.[32] This benefit of TG lowering should be weighed against the risk of severe myopathy, rhabdomyolysis and acute renal failure and should be avoided in patients with renal or hepatic failure. The combination of low dose statin (e.g. simvastatin 10 mg/day) combined with niacin (less than 2g/day) can produce reduction in total cholesterol, LDL cholesterol and TG by 24%, 29% and 31% respectively with an increase in HDL cholesterol by 31%.[36] However, it may worsen hyperglycaemia by increasing insulin resistance[36] and hence requires frequent monitoring of blood glucose levels.[37] Triple drug therapy with lovastatin, niacin and resins can lower LDL cholesterol by 70-80% but has not been studied in diabetics.[38]

Other lipid lowering drugs

(a) Omega 3 fatty acids

Omega 3 fatty acids are primarily used in the treatment of marked hypertriglyceridaemia when fibric acid derivatives alone are not effective.[30] However, they can also be combined readily with statins. These compounds have minimal effect on raising HDL cholesterol or reducing LDL cholesterol levels.[39] The daily dose is 2 to 4g/day; at higher dosage there may be worsening of glycaemic control.[40] Presently there is no clinical evidence that reduction in CHD event occurs in diabetic patients after treatment with Omega 3 fatty acids, but their use is supported by epidemiological

evidence that increased dietary consumption of fish is associated with lower risk of CHD.[39]

(b) Estrogen

In postmenopausal women with type 2 diabetes, estrogen therapy increases HDL cholesterol levels, decreases LDL cholesterol and Lp(a) levels which is comparable with those achieved by treatment with simvastatin 10 mg per day.[30] However, it simultaneously increases triglyceride levels and reduces LDL particle size. The data for cardiovascular risk reduction in diabetic females are very limited and benefits remain uncertain.[41] Estrogen replacement therapy needs to be used with some caution in women with diabetes, because of the risk of the aggravating pre-existing hypertriglyceridaemia. Estrogen is better avoided if the fasting triglycerinde levels exceeds 3.0 mmol/L (272 mg/dl).[30]

Conclusion

In 60 to 80% of diabetic patients, dyslipidaemia is a major contributor to atherosclerosis. An overwhelming amount of data provides evidence of reduction in total and in particular, cardiac morbidity and mortality in diabetic patients by aggressive lipid optimising therapy.[42] The angiographic regression studies have demonstrated that the inexorable progress of atherosclerosis can be slowed, arrested and in some cases reversed by lipid lowering therapy.[43] Thus aggressive management of dyslipidaemia with behavioural modification and lipid lowering drugs is an essential component of diabetes management.

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