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Full Length Research Paper

An overview on management of diabetic dyslipidemia

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Type 2 diabetes mellitus (DM) has recently been described as "coronary risk equivalent". Lipoprotein metabolism disorder in type 2 DM is known as diabetic dyslipidemia. Dyslipidemia contributes to a substantial percentage in cardiovascular mortality and morbidity in diabetic patients. National Cholesterol Education Program (NCEP) and American Diabetic Association (ADA) have provided recent guidelines for early diagnostic and therapeutic approaches to contain this health hazard. Diabetic patients tend to have higher serum levels of triglycerides (TGs), lower high-density lipoprotein cholesterol (HDL-C), and similar serum values for low-density lipoprotein cholesterol (LDL-C) when compared with non-diabetic patients. However, diabetic patients tend to have a higher concentration of smaller and denser LDL particles, which are associated with higher coronary heart disease (CHD) risk. Current recommendations are for a LDL-C goal of less than 100 mg/dl (an option of less than 70 mg/dl in very high-risk patients), a HDL-C goal greater than 40 mg/dl for men and greater than 50 mg/dl for women, and a triglyceride goal less than 150 mg/dl. Non-pharmacologic interventions (diet and exercise) are first-line therapies and are adjuvant to the pharmacologic therapy when necessary. Reduction in serum LDL levels will reduce the circulating levels of smaller and denser LDL particles. Thus lowering LDL-C level is the first priority in treating diabetic dyslipidemia. Statins are the first drug of choice, followed by resins, ezetimibe, fenofibrate, niacin and others. If a single agent is inadequate to achieve lipid goals, combinations of the preceding drugs may be used.

Key words: Diabetic dyslipidemia, diabetes mellitus, coronary heart disease.

INTRODUCTION

Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemia may be manifested by elevation of the total cholesterol, the low-density lipoprotein cholesterol (LDL-C) and the triglyceride (TG) concentrations, and a decrease in the high-density lipoprotein cholesterol (HDL-C) concentration in the blood. The association of dyslipidemia with type 2 diabetes mellitus (DM) as co-morbidity for cardio-vascular events leading eventually to a high rate of mortality has been a growing concern for the medical fraternity. Lipoprotein (a) [Lp(a)], the smaller and denser fraction of LDL-C, because of its profound athero-genecity, is an emerging risk factor for coronary heart disease (CHD) (American Diabetes Association, 2004). This Lp(a) has a propensity for atherogenesis appearing to be approximately twice as high in type 2 DM as compared to non-diabetics (Vakkilainen et al., 2003). There has been 2 to 4 fold increased risk of CHD, cerebrovascular stroke, peripheral vascular disease events in type 2 DM and the mortality from cardiovascular complications remains as high as 75% in these patients. It has been debated whether patients with diabetes who have not had myocardial infarction (MIs) should be treated aggressively for cardiovascular risk factors as patients who have had MIs. In support of aggressive care are findings that diabetic patients without previous MIs

have as high a risk of death from CHD as non-diabetic patients who have had a previous MI. Adult Treatment Panel (ATP) III now defines diabetes as a CHD risk equivalent (Krentz, 2000; Haffner et al., 1998), evident from Figure 1. The relative risk for major CHD events is reduced by approximately 1% with every 1% reduction in LDL-C levels as depicted in the following graph (Grundy et al., 2004a) (Figure 2). This relationship is consistent with a large body of epidemiological data and with the data available from clinical trials of LDL-C lowering therapy. These data suggest that for every 30 mg/dl change in LDL-C, the relative risk for CHD is changed in proportion by about 30%. The Collaborative Atorvastatin Diabetes Study (CARDS) suggests that the subjects with type 2 DM could benefit from statin therapy to reduce cardiovascular disease (CVD) risk, even when they do not have high cholesterol (Colhoun et al., 2004). Hence, prompt identifi-cation and aggressive management of dyslipidemia in type 2 DM, aimed at achieving the recommended set goal by National Cholesterol Education Program (NCEP) in type 2 DM, have become a cornerstone of diabetic care. This article provides a review of the current literature supporting the recommendations for the management of dyslipidaemia among patients with type 2 diabetes, including new strategies involving newer agents and drug combinations that achieve good glycaemic and lipidaemic control that could potentially reduce the morbidity and mortality associated with type 2 diabetes.

Features of diabetic dyslipidemia

The most common pattern of dyslipidemia in type 2 DM is elevated TGs and decreased HDL-C levels. However, the concentration of LDL-C in type 2 diabetic patients is usually not significantly different from non-diabetic individuals. But, “modified” LDL-C in type 2 DM can promote athero-genesis. For example, non-enzymatic glycation may cause LDL-C to be rapidly internalized by macrophages, thus accelerating the process of atherosclerosis. Elevated glu-cose levels may also favor the production of oxidized LDL-C, the first step in the process of atherosclerosis (Curtiss and Witztum, 1985). These patients typically have
a preponderance of smaller and denser LDL particles Lp(a) which possibly increases atherogenecity, even though the absolute concentration of LDL-C is not significantly raised (Krauss, 2004). Type 1 DM by itself is seldom associated with any lipid abnormalities, until the nephropathy sets in, leading to elevated levels of total cholesterol, LDL-C, TGs, Lp(a) and reduced HDL-C level (Kreisberg, 1998).

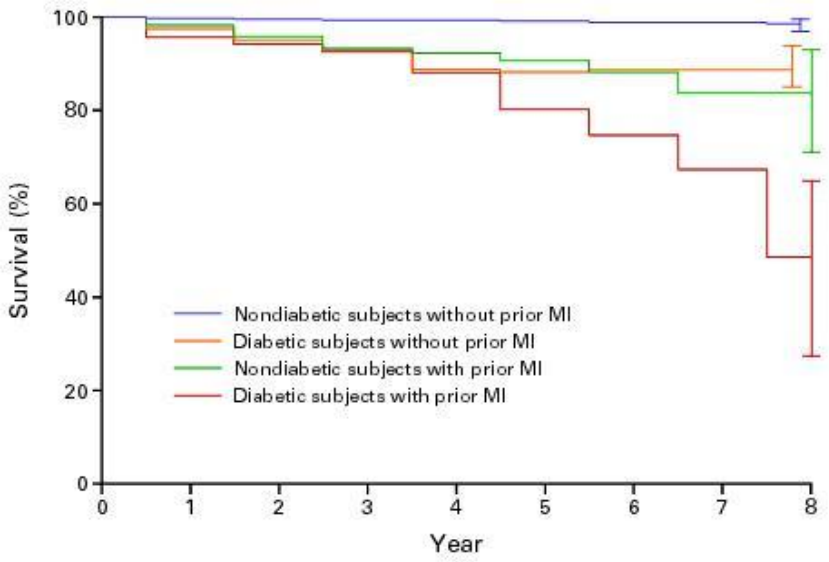
PATHOGENESIS OF DIABETIC DYSLIPIDEMIA

The pathogenesis of diabetic dyslipidemia is a complex phenomenon. Normally insulin inhibits lipolysis in adipose tissue by suppressing hormone sensitive lipase present in the cytosol of adipocytes, particularly visceral adipocytes. The insulin deficiency in diabetes reduces suppression of hormone sensitive lipase activity thereby increasing intra-cellular hydrolysis of TGs in the adipose tissue, conse-quently releasing free fatty acids (FFA) in the portal circulation. These FFA stimulate the assembly and secretion of very-low-density lipoprotein (VLDL; the major triglyceride ide-carrying lipoprotein particle) from the liver, resulting in excess circulating TG concen-tration (Ginsberg, 1996). The increase VLDL also results from reduced action of insulin on hepatocytes causing reduced suppression of VLDL production. The LDL-C does not appear to be secreted as such from either the liver or intestine; rather it seems to be formed from VLDL and possibly chylomicrons (Lewis et al., 1993). The formation of LDL from VLDL may contribute to the clinical phenomenon referred to as the "beta shift" (Mayes, 1977). An increase of LDL as hypertrigyceridemia resolves and because of its longer half-life, the LDL accumulates in plasma. TG-enriched LDL-C may undergo lipolysis resulting in increase in small and dense LDL-C particles Lp(a). The LDL-C particle size is reduced by increased hepatic lipase (present in the hepatic endothelium) activity. The low HDL-C in these patients results from reduced production, increased clearance or VLDL stimulating the exchange of cholesterol ester from HDL particles through cholesteryl ester transfer protein (CETP) (Figure 3).

BENEFITS OF TREATMENT OF DIABETIC DYSLIPIDEMIA: CLINICAL TRIAL EVIDENCE

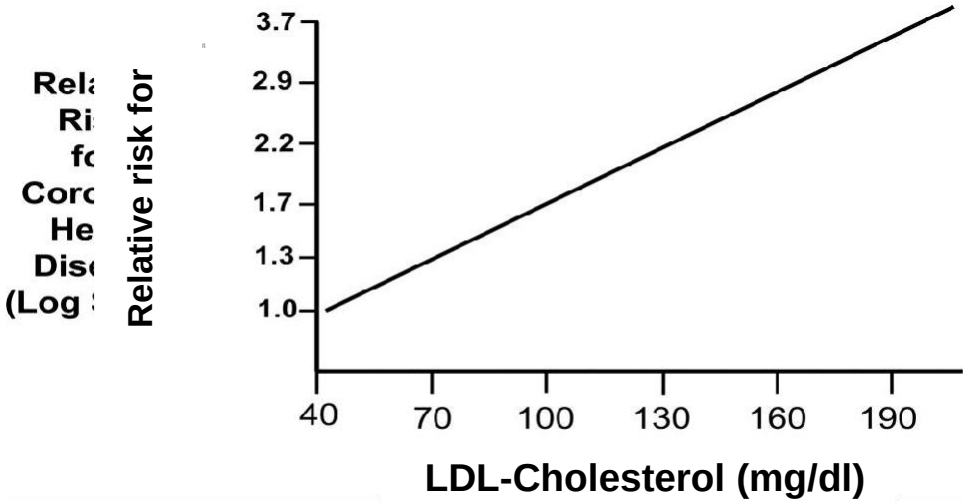
In the widely acclaimed popular Scandinavian Simvastatin Survival Study (4S) trial, simvastatin significantly reduced CHD incidence and total mortality in diabetic subjects with high LDL cholesterol or with previous clinical CHD (The Scandinavian Simvastatin Survival Study Group, 1994; Pedersen et al., 2000). In the Cholesterol and Recurrent Events (CARE) study, pravastatin reduced CHD incidence significantly in diabetic subjects with average LDL levels and with previous clinical CHD (Goldberg et al., 1998). In the Helsinki Heart Study, gemfibrozil was associated with a reduction in CHD in diabetic subjects without prior CHD (Frick et al., 1993). The recently completed Heart Protection Study (HPS) has been the largest study to date, enrolling and randomizing 5,963 patients over the age of 40 years with diabetes and total serum cholesterol more than 135 mg/dl (Collins et al., 2003). In this trial, patients with diabetes assigned to simvastatin had a 22% reduction in the event rate for major cardiovascular disease (Collins et al., 2003). In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), gemfibrozil was associated with a 24% decrease in cardiovascular events in diabetic subjects with prior cardiovascular disease, low HDL (<40 mg/dl) and modestly elevated triglycerides (Robins et al., 2001). Two recent trials (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm [ASCOT-LLA] with atrovastatin 10 mg and Antihypertensive and Lipid-

Fig. 1: Diabetics without prior MI face similar risks as nondiabetics with prior MI



Circulation. 2004;109:855-860

Figure 1. Diabetics without prior MI face similar risks as non-diabetics with prior MI



Circulation 2004;110:227-239

Figure 2. Log-linear relationship between LDL-C levels and relative risk for CHD.

Lowering Treatment to Prevent Heart Attack Trial [ALLHAT] with pravastatin 10 mg) indicated that further reduction of the LDL-C threshold resulted in additional benefits for patients in the moderately high-risk category (Sever et al., 2003). A meta-analysis of four large trials revealed that the high-dose statin therapy significantly improves cardiovascular outcomes as compared to the standard low-dose one (The Scandinavian Simvastatin Survival Study Group, 1994). The ASCOT-LLA and Collaborative Atorvastatin Diabetes Study (CARDS) suggests people with type 2 diabetes could benefit from statin therapy to reduce CVD risk, even when they do not have high cholesterol (Pedersen et al., 2000; Goldberg et al., 1998) (Table 1).

SCREENING PROTOCOL

A definitive screening for dyslipidemia is significantly important for its early detection and management to curb

Table 1. Clinical trial evidence (Titel should be completed).

Study	Drug (mg/day)	CHD event Reduction (%)
4S	Simvastatin 20-40	55
CARE	Pravastatin 40	25
HPS	Simvastatin 40	22
VA-HIT	Gemfibrozil 600	24
ASCOT-LLA	Atrovastatin 10	23
ALLHAT	Pravastatin 10	11
CARDS	Atrovastatin 10	36

the associated high morbidity and mortality in adults. Every adult aged 20 years or above should have a fasting lipoprotein profile every 5 years. It is preferable to perform annual lipid profile in all diabetics and if the values remain normal, assessment may be repeated every 2 years. In children with diabetes, consideration should be given to measure lipoproteins after age 2 years, as suggested by the NCEP (Haffner, 1998). Risk factors contributing to the early onset of CHD in children and adolescents include elevated LDL-C levels; family history of CHD, cardiovas-cular disease (CVD), or peripheral vascular disease before age 55 years, smoking, hypertension, HDL-C levels less than 35 mg/dl, obesity, physical inactivity, and diabetes (Frick et al., 1993). The potential harms and benefits of routinely screening for lipid disorders in children, adole-scents, or adults as old as 20 years are not clear, according to the US Preventive Services Task Force (USPSTF) statement published in the July 9, 2007; issue of pediatrics (American Diabetes Association, 2004).

RECOMMENDED TREATMENT TARGETS

The recommendations for treatment of elevated LDL-C generally follow the guidelines of both NCEP and a recent American Diabetes Association (ADA) consensus development conference. The Adult Treatment Panel III (ATP III) of the NCEP issued an evidence-based set of guidelines on cholesterol management in 2001. Since the publication of ATP III, 5 major clinical trials of statin therapy with clinical end points have been published. The ADA has set desirable LDL-C, HDL-C, and triglyceride levels as <100 mg/dl, >40 mg/dl in men, >50 mg/dl in women, and <150 mg/dl, respectively. The primary treatment strategy, as in the NCEP guidelines, is LDL-C lowering to <100 mg/dl. The recommended LDL-C level to start pharmacological therapy is >100 mg/dl in individuals with established CHD and >130 mg/dl in those without CHD. However, the 2005 recommendations now also state that "statin therapy to achieve an LDL-C reduction of ~30% regardless of baseline LDL-C levels may be appropriate." (Prisant, 2004; Grundy et al., 2004b).

Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. This has 3 main areas of focus: diet, exercise, and weight reduction. Dietary recommendations consist of reduction of saturated fats (<7% of total calories), a low intake of cholesterol (<200 mg/day) otherwise known as NCEP step 2 diet. ADA suggests either a dietary increase in carbohydrate or monounsaturated fat to compensate the reduction in saturated fat. A moderate physical activity is encouraged because it can improve cardiovascular fitness and coronary blood flow, reduce VLDL, increase HDL-C, lower blood pressure, reduce insulin resistance and decrease LDL-C. The ADA recommends aerobic exercise at 50 to 70% maximum O2 uptake for 20 to 45 min, atleast 3 days per week (American Diabetes Association, 2001).

The ADA has assigned the priorities for lowering lipids and lipoproteins as per the following pattern (Robins et al., 2001). The first priority is the lowering of LDL-C; second priority is the lowering of triglyceride levels and third priority is raising levels of HDL-C. The lowering of LDL-C by statins is considered as the first priority because the clinical trials (4S and CARE) showed the effectiveness of statins in reducing CHD in diabetic subjects more convincing than for the Helsinki study with gemfibrozil and also, the safety record of the statins with regards to total mortality is better than that of the fibric acids.

According to the ATP III algorithm, persons are categorized into 3 risk categories (Tables 2 and 3): (1) established CHD and CHD risk equivalents, (2) multiple (2+) risk factors, and (3) zero to one (0 - 1) risk factor. CHD risk equivalents include non-coronary forms of clinical atherosclerotic disease, diabetes, and multiple (2+) CHD risk factors with 10-year risk for CHD >20%. All persons with CHD or CHD risk equivalents can be called high risk. The goal for LDL-lowering therapy in high-risk patients is an LDL-C level <100 mg/dl. According to ATP III, for a baseline or on-treatment LDL-C <100 mg/dl. For all high-risk patients with LDL-C levels ≥100 mg/dl, LDL-lowering dietary therapy should be initiated. When baseline LDL-C is ≥130 mg/dl, an LDL-lowering drug should be started simultaneously with dietary therapy. However, LDL-lowering drugs were not mandated if the baseline LDL-C level is in the range of 100 to 129 mg/dl.

The current ATP III of the NCEP recommendations is (NCEP, 2002):

(1) In high-risk persons, the recommended LDL-C goal is <100 mg/dl, but when risk is very high, an LDL-C goal of <70 mg/dl is a therapeutic option, on the basis of available clinical trial evidence.
(2) ATP III introduced a new secondary target of therapy, namely, non-HDL-C (VLDL, LDL) in patients with elevated triglycerides (>200 mg/dl). The non-HDL-C goal is 30 mg/dl higher than the LDL-C goal.
(3) Although the potential benefit of HDL-C raising therapy

Table 2. LDL goals recommended by the ADA in diabetic patients.

Patient profile	Medical nutrition	Drug	
	Initiation level (mg/dl)	Initiation level (mg/dl)	LDL-C level (mg/dl)
Pre-existing CVD	>100	>100	<100
Absence of CVD	>100	>130	<100

Diabetes Care. 26:S83-S86, 2003.

Table 3. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories (ATP III).

Risk category	LDL goal (mg/dl)	Initiate TLC (mg/dl)	Initiate drug therapy (mg/dl)
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100 - 129:drug optional)
2+Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10 - 20%: ≥130; 10-year risk <10%: ≥160
0-1 Risk factor	<160	≥160	≥190 (160 - 189: LDL-lowering drug optional)

Circulation. 2004; 110:227-239.

Table 4. Doses of Currently Available Statins Required to Attain an Approximate 30% to 40% Reduction of LDL-C Levels (Standard Doses)*.

Drug	Dose (mg/day)	LDL Reduction (%)
Atorvastatin	10‡	39
Lovastatin	40‡	31
Pravastatin	40‡	34
Simvastatin	20-40‡	35-41
Fluvastatin	40-80	25-35
Rosuvastatin	5-10‡	39-45

*Estimated LDL reductions were obtained from US Food and Drug Administration package inserts for each drug.
‡All of these are available at doses up to 80 mg. For every doubling of the dose above standard dose, an approximate 6% decrease in LDL-C level can be obtained. ŦFor rosuvastatin, doses available up to 40 mg; the efficacy for 5 mg is estimated by subtracting 6% from the Food and Drug Administration-reported efficacy at 10 mg. Circulation. 2004; 110:227-239.

has evoked considerable interest, current documentation of risk reduction through controlled clinical trials is not sufficient to warrant setting a specific goal value for raising HDL-C. Recent lipid-lowering drug trials provide no new evidence in this regard.

Lipid-lowering therapy in the management of diabetes: Current recommendations

After initial trial of diet therapy, drugs become the next important means to achieve the set and said goals (Tables 4 and 5).

HMG CoA reductase inhibitors (Statins)

These reduce LDL-C by 18 to 55% and TG by 7 to 30% and raise HDL-C by 5 to 15%, and hence are considered to be very effective. They are known to produce usually gastric intolerance apart from myopathy and elevated hepatic transaminases. Hence, they are contraindicated in liver affections while drug interactions must be taken care of during their usage. Their definitive benefits have been documented in reducing major coronary events, CHD mortality, cerebral stroke, procedures like PTCA/CABG and thereby decreasing overall mortality (American Diabetes Association, 2008; Vijan and Hayward, 2004).

Bile acid sequestrants

Their major action is directed to reducing LDL-C by 15 to 30%, raising HDL-C by 3 to 5% while sometimes increasing TG. They can cause gastrointestinal disturbances and also interfere with absorption of many drugs. They must be avoided in the presence of dysbetalipoproteinemia or raised TG especially when the value exceeds 400 ml/dl (Wong, 2001).

Nicotinic acid

It lowers the LDL-C by 5 to 25%, TG by 20 to 50% and raises HDL-C by 15 to 35%. In fact, it is one of the strongest tools to raise favourable HDL-C. But it causes flushing, hyperglycemia, hyperuricemia in addition to upper gastrointestinal distress and hepatotoxicity. It is contraindicated in peptic ulcer, severe gout and liver disease (Tavintharan and Kashyap, 2001).

Table 5. Non-statin drugs for management of lipid disorders in diabetes.

Drug	Doses
Fibrates	
Gemfibrozil	600 mg daily
Fenofibrate	200 mg daily
Clofibrate	200 mg daily
Bile acid sequestrants	
Colestipol	l5 - 20 g daily
Cholestyramine	4 - 16 g daily
Nicotinic acid	
Niacin	1.5 - 3 g daily
Cholesterol absorption inhibitor	
Ezitimibe	10 mg daily

Fibric acids

These decrease LDL-C by 5 to 20% when the value of TG is normal, but with high value of TG, contrarily LDL-C may be increased because of improved VLDL metabolism. TG levels are lowered by 20 to 50% while HDL-C may be raised to 10 to 20%. They can cause dyspepsia, gall stone and myopathy. Severe renal and hepatic impairment are contraindication for prescribing these acids (Bloomfield et al., 1999; Tsimihodimos et al., 2005).

Ezetimibe

Ezetimibe, a selective cholesterol absorption inhibitor, blocks the synthesis of a key protein in the intestinal villi, thus preventing the absorption of dietary cholesterol. By itself, the drug has been shown to reduce modestly the serum levels of LDL-C, but it works synergistically when combined with a statin. The action of ezetimibe 10 mg plus a 10 mg dose of a statin is equivalent to that of a statin alone at higher doses, such as 80 mg of simvastatin or 40 mg of atorvastatin. It is used (10 mg daily) to reduce the amount of total cholesterol, LDL cholesterol and also, there are no differences in liver or muscle-related side effects while combined with statin therapy (Bays, 2002).

Rosuvastatin

Compared to other HMG-CoA reductase inhibitors, rosuvastatin possesses the highest bonding interactions with HMG-CoA reductase, resulting in the most potent inhibition of cholesterol synthesis. The half-life of rosuvastatin is approximately 20 h, which is longer than the other HMG-CoA reductase inhibitors. An advantage with rosuvastatin is that it is not significantly metabolized by the liver. Rosuvastatin is primarily eliminated through biliary excretion (90%) and found unchanged in the feces, with the remainder of elimination occurring in the urine. The FDA-approved dosage range of rosuvastatin is 5 to 40 mg daily; however, the 40 mg dose should only be used in patients who do not reach their LDL-C goal with the 20 mg dosage. The recent JUPITER trial indicated a reduction in incidence of total stroke by 48% in apparently healthy individuals with elevated highly sensitive c-reactive protein (hsCRP) and low to normal LDL-C (American Diabetes Association, 2008). Although more potent, it can cause potentially serious kidney toxicity that is not seen with the other statins. It is the only statin that caused rhabdomyolysis, a life-threatening adverse drug reaction, in pre-approval clinical trials (Ridker et al., 2008; Vaughan and Gotto, 2004; Davidson, 2002).

Omega-3 fatty acids

Fish oil preparations containing omega-3 fatty acids have been proven useful in reducing triglyceride levels in patients with diabetes although they are only indicated for patients with severe hypertriglyceridaemia and/or chylomicronaemia and for patients whose triglycerides remain elevated despite alternative therapies (Kris-Etherton et al., 2002).

CETP (cholesteryl ester transfer protein) inhibitors

An emerging therapeutic avenue for the management of dyslipidemia is inhibition of CETP, given that elevated CETP levels appear to be associated with progressive atherosclerosis in patients with type 2 diabetes. Two CETP inhibitors, JTT-705 and torcetrapib, are currently in the early stages of development and the results of both monotherapy and combination therapy are conflicting (Brousseau et al., 2006).

Rimonabant

A cannabinoid receptor blocker significantly reduces weight and waist circumference and improves dyslipidemias in overweight and obese patients with or without diabetes. It decreases TG and increases HDL levels (Hollander, 2007).

Other antidiabetic agents

Insulin therapy itself, through its direct effect on the adipocytes and the liver, can lower TG concentrations, significantly but have minimal impact on HDL levels (Ginsberg, 2000). Exenatide, a glucagon like peptide one

Table 6. Following would be a practical approach to the pharmacologic treatment of lipid disorders in diabetes.

Lipid disorder	1st Choice	Alternate or add on	Other consideration
High LDL-C	Statin	Ezetimibe	Niacin
Low HDL-C	Fibrate	Niacin	Statin, thiazolidinediones
High TGs	Fibrate	High-dose statin	Niacin, pioglitazone and/or insulin
Combined hyperlipidemia	High-dose statin	Statin+fibrate	Statin + niacin

Endocrinol Metab Clin N Am. 2005; 34:36.

(GLP-1) analogue increases HDL-C and decreases LDL-C, probably an indirect effect secondary to its weight reduction (Klonoff et al., 2008). Metformin, recent meta-analysis of 41 randomized, controlled clinical trials assessing the effects of metformin on the lipid profile in patients with type 2 diabetes concluded that metformin has no intrinsic effect on triglycerides and HDL-C and any reductions in LDL-C, although statistically significant, are relatively small (Wulffele et al., 2004).

Pioglitazone as monotherapy in patients with type 2 diabetes provides significant improvements in glycemic control, while also causing significant decreases in plasma triglycerides and increases in HDL-C when compared with placebo (Winkler et al., 2002).

Roseglitazone, the benefits of rosiglitazone monotherapy on diabetic dyslipidemia are less apparent and the only clear advantage appears to be an increase in HDL-C levels of 14 to 18%. Triglycerides appear to be unaffected by rosiglitazone and LDL-C increased by 9.5% among patients treated with 2 mg twice daily to 18.3% among patients treated with 8 mg once daily (Brunzell et al., 2001).

COMBINATION THERAPY AND FACTS

Often monotherapy is not sufficient to completely normalize the lipid profile. Currently, there are no randomized controlled trials demonstrating that combination therapy reduces cardiovascular disease to a greater extent than monotherapy. Use of combination therapy should be considered in several situations. First, combination therapy is useful in those patients who are unable to reach their target with just one drug. As mentioned previously, doubling the dosage of statins will only decrease LDL levels by an additional 5 to 10% and may not be enough to reach the goal. However, by using combination therapy, the addition of another lipid-regulating agent with a different mechanism of action may lower LDL levels by another 20 to 25%. Second, patients with diabetes often have abnormalities in more than one type of lipid particle and have high LDL levels as well as low HDL levels and high triglyceride levels. Most lipid-lowering drugs partially correct lipid abnormalities or achieve target values. For example, statins are powerful agents to lower LDL levels. However, if a patient also has a high triglyceride level or low HDL level, adding a second agent such as a fibrate or niacin should be considered. Third, occasionally, maximum dosage escalation cannot be achieved because of adverse effects. Since the occurrence of adverse effects often correlates with the dosage, small dosages of lipid-regulating agents from two different classes can be used together to reach goal (Table 6).

When using combination therapy one must be aware that the addition of either fibrate or niacin to statin therapy increases the risk of myositis. The increased risk of myositis is greatest when gemfibrozil is used in combination with statins. Statins plus bile acid resins or ezetimibe can achieve greater than 50% reduction in LDL-C, with little or no increase in adverse effects. Fibrates, niacin, and omega-3 fatty acids, when added to statins, can reduce triglycerides, increase HDL-C, and reduce non-HDL-C to a greater extent than statin monotherapy. Conclusions regarding ezetimibe/statins combinations should not be made until the three large clinical outcome trials will be completed within the next 2 to 3 years (Tenenbaum et al., 2008). Majority of LDL-C lowering effect occurs at the lowest statin dose and side effects are dose dependent. Hence, to start with, the lowest possible dose is recommended (Jones et al., 1998). The combination of statins with nicotinic acid is extremely effective in modifying diabetic dyslipidemia (with the largest increases in HDL-C levels), but this significantly worsen hyper-glycemia. Thus, this combination should be used with extreme caution like using low doses of nicotinic acid (<=2 g of nicotinic acid per day) with frequent monitoring of blood glucose levels. It should also be noted that the higher doses of statins may be moderately effective at reducing triglyceride levels (although not necessarily at raising HDL levels) and thus may reduce the need for combination therapy. The elevation of liver enzymes more than 3 times the upper limit of normal is found in less than 1.5% cases while significant myopathy in less than 0.3%, with statins (Heart Protection study Collaborative Group, 2002). Recently, it is demonstrated that gemfibrozil and fenofibrate differ in their effects on statin pharmacokinetics. A recently conducted national survey reported the prevalence of rhabdomyolysis to be approximately 10 times more with statin plus fenofibrate and about a 100 times more likely with statin plus gemfibrozil treatment compared to statin alone (Jones, 2005). Thus fenofibrate is preferred to gemfibrozil for use in combination therapy with statins. Fenofibrate is more likely to increase serum creatinine levels than gemfibrozil and should be avoided in patients with renal disease; in whom, the combination of statin and niacin probably is safer than a statin-fibrate

regimen.

The safety profile of combination lipid lowering therapy is acceptable, if the global CHD risk of the patient is high, thus producing a favorable risk to benefit ratio. Careful surveillance of hepatic transaminases, avoidance of gemfibrozil in statin-fibrate combinations, and awareness of statin-concomitant drug interactions is the key to safe and efficacious use of combination lipid lowering drug therapy (Vasudevan and Jones, 2006).

Clinical approach in drug selection

The ADA provides recommendations and priorities for treatment of dyslipidemia specifically for patients with diabetes. Although patients with diabetes have characteristically low HDL levels and high triglyceride levels with "normal" LDL levels, the priority should still lie in lowering LDL levels since many large clinical trials in the general population repeatedly have shown that lowering LDL levels will decrease CHD events. Resins, ezetimibe, niacin, or combinations are used as alternatives. For those patients with low HDL and/or high triglyceride levels, fibrates are the first choice. However, the increased risk of myopathy with a statin-fibrate combination must be considered. The combination is to be avoided in patients with diabetic nephropathy. Niacin, fish oil, or combinations are used in addition or as alternatives if the goal is not achieved. Many patients with diabetes will have abnormalities in all lipid particles. They may have high LDL levels, and at the same time, have low HDL and high triglyceride levels. In this scenario, treating LDL is still the first priority. After the LDL goal is reached, treatment for low HDL and high triglyceride levels should be considered. One exception is for those with extremely high triglyceride levels (>500 mg/dl) who are at risk for pancreatitis. For patients with triglyceride levels greater than 500 mg/dl, triglycerides should be treated first (Knopp, 1999).

A significant number of patients with diabetes will require combination therapy. Most combinations are safe and effective, except as previously stated. Benefits of combina-tion therapy should be carefully weighed against the risks. A complete review of the patient's drug regimen along with a medical history should be performed. To minimize the occurrence of myotoxicity in these patients, clinicians should ensure that there are no interactions with drugs that can decrease statin clearance (Figure 4).

Monitoring of therapy

Summary of National Lipid Association Statin Safety Recommendations (Kapur and Musunuru, 2008).

Muscle effects

Pretreatment measurement of creatine kinase (CK) levels is generally not necessary unless an individual is at high risk.

(1) Routine measurements of CK levels are unnecessary in asymptomatic patients.
(2) Counsel patients on the possibility of muscle discomfort while on statin therapy and the importance of reporting symptoms like muscle ache.
(3) In symptomatic patients, CK levels should be measured: (a) If CK levels <10 times the upper limit of normal (ULN) then statin therapy may be continued or doses reduced with close monitoring of symptoms; (b) If CK levels >10,000 IU/L or above 10 times the ULN, then admit for intravenous (IV) hydration therapy, monitoring of renal function, and treatment of rhabdomyolysis; (c) Irrespective of CK levels, if muscle symptoms are intolerable, statin therapy should be discontinued with possible reinstitution of a different agent or lower dose once patient becomes asymptomatic; (d) If symptoms recur, alternative therapies should be considered.

Hepatic effects

(1) Measure serum hepatic transaminase levels before initiating therapy, 12 weeks after starting therapy, after a dose adjustment, and periodically thereafter.
(2) Monitor for signs of potential hepatotoxicity such as jaundice, malaise, fatigue, and lethargy. If present, measure transaminase levels, fractionated bilirubin levels, and liver function tests.
(3) In asymptomatic patients, if serum hepatic transaminase levels are between 1 and 3 times the ULN, then consider continuing statin therapy with close follow up testing.
(4) If serum hepatic transaminase levels increase >3 times the ULN, then reduce the statin dose or discontinue treatment while ruling out other possible etiologies.
(5) If objective evidence of liver injury is documented, then discontinue the statin and refer the patient to a gastroenterologist.

Renal effects

(1) Routine measurements of serum creatinine and proetinuria are not necessary for patients on statins.
(2) Pre-treatment baseline creatinine levels may be helpful in identifying patients with underlying renal disease who may be at risk for higher muscle toxicity.
(3) If creatinine levels increase while on statin therapy, an adjustment in statin dosing may be required.
(4) If proteinuria is detected, consider adjusting the statin dose.
(5) Any perturbation of renal indices should warrant further investigation of other non-statin related causes.
(6) In patients with chronic kidney disease, statin therapy may be initiated with close attention to dose adjustments in moderate to severe renal disease.

Risk factors for muscle toxicity include: concomitant therapy with fibric acid derivatives, erythromycin, or azole antifungals, advanced age, small body habitus, worsening renal function, ongoing infection, trauma such as recent surgery, alcohol abuse, and untreated hypothyroidism.

CONCLUSION

All diabetic patients should be treated aggressively for the prevention of CVD, because diabetic patients without previous MI have as high a risk of MI as non-diabetic patients with previous MI. Current ADA and NCEP guidelines recommend aggressive treatment for dyslipidemia in diabetic patients, particularly in those with elevated LDL-C levels which remains the first priority, but abnormalities in HDL-C and TG levels also should be treated aggressively. Tight glycemic control achieved with diet, exercise, and some antidiabetic agents may substantially improve the lipid profile and reduce the risk of CVD in some patients. However, most patients will require the use of intensive lipid-lowering therapy to reduce their cardiovascular risk, most commonly with one of the statins or fibric acid derivatives. Finally, since combination therapy is safe for most patients if used judiciously, it should be considered for all those who are unable to meet their goals with monotherapy.

FUTURE DIRECTIONS

The third generation statin, rosuvastatin, has demonstrated reasonable clinical efficacy and safety in several clinical trials. Safety issues surrounding the use of high-potency statins remain of paramount concern. Future studies involving rosuvastatin/fenofibrate combination therapy and the recently announced combination of rosuvastatin with a next generation fenofibrate (ABT-335) will provide further insight into the efficacy of dual-targeted therapy on both LDL-C and HDL-C profiles.

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