Abstract
Diabetes and dyslipidaemia are two common comorbid conditions encountered in clinical practice. This review discusses the screening, investigations, non-pharmacological and pharmacological management of dyslipidaemia in type 2, type 1, and pre-diabetes, with a view to improving cardiovascular outcomes. The paper highlights certain simple dos and don'ts which may be useful for our cultural and clinical setting.

Keywords: Diabetes, Dyslipidemia, Cardiovascular outcomes.

Type 2 Diabetes
Type 2 Diabetes is termed as an angina equivalent. People with diabetes and no history of myocardial infarction have a cardiovascular risk equivalent to those without diabetes and a history of MI. Diabetes increases the risk of cardiovascular disease (CVD) by five times in women, and three fold in men.

Risk factors or postulated mechanisms for the rapid development of vascular disease in diabetes include hyperglycaemia, hypertension, low HDL-C, high triglyceride levels, small dense LDL-C, a pro coagulant state, and a pro-inflammatory milieu. It stands to reason, therefore, that lipid management is an essential part of diabetes care.

Screening and Investigations
People with diabetes are classified as high risk patients for vascular events. Hence, irrespective of presence or absence of other risk factors on history (age, gender, smoking, hypertension, family history) or examination (obesity, hypertension, polycystic ovary syndrome in women), they should be screened for dyslipidaemia. Because of this blanket recommendation, global risk assessment tools such as the Framingham Risk Assessment Tool, SCORE (Systematic Coronary Risk Estimation) charts, and Reynolds Risk Score are actually not of much use in people with diabetes, even when their LDL-C levels have been controlled, by reflecting the LDL particle number (rather than size). In case further risk stratification is required, inflammatory markers such as hsCRP and Lp-PLA2 may be checked. However, routine assessment of these markers is not recommended for either screening, pre-treatment characterization, or follow up of treatment.

Calculation of non-HDL-C is also necessary in these patients. Apo-B levels should be tested in type 2 diabetes patients if possible. This is necessary as the apoB or apoB-apoA1 ratio helps assess residual risk in people with diabetes, even when their LDL-C levels have been controlled, by reflecting the LDL particle number (rather than size). In case further risk stratification is required, inflammatory markers such as hsCRP and Lp-PLA2 may be checked. However, routine assessment of these markers is not recommended for either screening, pre-treatment characterization, or follow up of treatment.

Evaluation of body mass index and other anthropometric measurements, focusing on central obesity, measurement of blood pressure, and monitoring of glycaemic control, is indicated as per routine practice. Increased waist circumference is a simple, yet effective, tool for detecting high risk patients. Polycystic ovarian syndrome should be ruled out in women with dyslipidaemia and other features of Metabolic Syndrome.

Assessment and relatively more frequent follow up of lipid levels in indicated in the following clinical or laboratory situations:

1. Clinical
   - Rise in blood pressure
• Worsening of glycaemia
• Gain in weight

2. Drug-related
• Addition
• Discontinuation
• Significant change in dose of any
• Anti-hypertensive, anti-diabetic, anti-obesity drug, or other drug expected to have a(n):
• Effect on lipid levels
• Drug-drug interaction with lipid-lowering therapy

3. Biochemical
• worsening of HbA1c
• Rise in liver enzymes

Goals of Therapy
Lipid goals are similar for high risk individuals with and without diabetes. The primary target is LDL-C, while non-HDL-C and apoB are secondary targets. The CSI guidelines recommend a target of LDL-C < 100mg% in all persons with uncomplicated diabetes. In people with diabetes and one or more extra risk factor (such as existing CVD; family history of premature CVD; smoking), the target is revised to <70mg%.

While therapy is oriented towards an LDL-C based target, other lipid parameters should also be taken into consideration. In both men and women, HDL-C should be maintained >40mg%. There is no clear-cut advantage of trying to increase HDL-C levels to very high values in people with diabetes. An isolated low HDL-C value in a person with diabetes and an otherwise normal lipidogram does not warrant pharmacotherapy.

In people with diabetes, the non-HDL-C goal is 130mg% for uncomplicated diabetes and 100 mg% for those with additional risk factors. Ideal apoB level is <90% in uncomplicated diabetes and <80% in those with extra risk factors. In all persons with diabetes, a triglyceride level of <150mg % is aimed for. These goals are global, i.e., for both genders and for all adults. In children and adolescents, acceptable LDL-C level are relaxed to 110mg%.

Non-pharmacological Therapy
Management of dyslipidaemia in diabetes is similar to that in people without diabetes. Nonpharmacological therapy viz physical activity, cessation of smoking, and medical nutrition therapy are important aspects of treatment.

A minimum of 30 minutes of moderate intensity physical activity every alternate day is recommended to improve lipid levels and insulin sensitivity. Resistance exercises of similar duration, twice a week, should also be performed. Weight reduction improves insulin sensitivity, and reduces lipid levels. Maximal effect is observed on triglycerides (20-30%), with HDL-C (0.4mg% increase per kg body weight lost) and LDL-C (0.8mg % fall per kg body weight loss) showing lesser benefit. Exercise per se has significant effects on HDL-C (3.1-6mg% increase in HDL-C with 1500-2200Kcal/week of aerobic exercise), but not on LDL-C. Folk dances, such as the vigorous bhangra, dhammaal and jhoomer, and traditional sports like kabaddi should be promoted as acceptable, low cost, indigenous forms of healthy exercise.

Diet prescriptions for diabetes and for dyslipidaemia are usually concordant with each other. The 2 minute weight + 10 diet can be utilized in resource-challenged clinical settings with shortage of trained manpower. A diet rich on fruits and vegetables (≥5 servings/day), grains (≥6 serving/day, with at least 2 servings as whole grains), fish/lean meat is recommended: this mimics a traditional Pakistani diet. Low glycaemic index and high fiber foods have a beneficial effect on lipidaemia, and should be encouraged. Food should be rich in fiber (10-25g of soluble fiber) and plant stanols/sterols (2g/day): this, too, reflects the advantages of traditional cuisine. However, a lipid-friendly diet differs from the traditional Pakistani kitchen offering in its emphasis on restriction of saturated fats, trans fats and cholesterol.

Dietary fructose leads to hypertriglyceridaemia if taken in excess of 10% of total energy intake, in spite of its low glycaemic index. A careful dietary review of all persons with hypertriglyceridaemia, focusing on fructose intake, is suggested.

Pharmacological Therapy
Drugs should be initiated in all persons with diabetes and dyslipidaemia, and in normolipaemic persons aged >40 years who have concomitant diabetes. Eulipaeic obesity is not an indication for pharmacological lipid lowering therapy. Lifestyle modification, consisting of physical activity and nutrition, is indicated in all persons with dyslipidaemia and diabetes.

Statins
The choice of drug therapy is similar in dyslipidaemic persons with and without diabetes. The CSI guidelines strongly recommend statin therapy despite the fact that certain studies document a rise in incidence of diabetes with these drugs. Meta analysis has shown that statin use is linked to a higher (9%) risk of development of new-onset diabetes, especially in older persons. The risk of diabetes is not linked to body mass index or lipid-lowering efficacy of statins. However, the risk: benefit ratio of statins is tilted in favour of drug use.

The choice of statin in diabetes is similar to that in people without diabetes. Glucose neutral effects have been reported for pravastatin. Pitavastatin use has been reported to be
devoid of the adverse effects on glycaemia that are reported with atorvastatin. Pitavastatin, in fact, demonstrated a beneficial effect on HbA1c in subjects with diabetes who enrolled in the LIVES study. The metabolic pathways for various statins differ, and this may explain differential effects on glycaemic control. Pitavastatin is minimally metabolized by the CYP3A4 isoenzyme, unlike other statins, and this may explain its glucose-neutral character. Atorvastatin is thought to suppress glucose transporter GLUT4 expression in 3T3-L1 adipose cells by blocking isoprenoid synthesis. Simvastatin has been shown to inhibit glucose-induced insulin secretion through blockade of L-type Ca2+ channels in β-cells. Cytotoxic effects on the β-cell have also been reported for atorvastatin. Another postulated mechanism is through activation of SREBPs.

People with diabetes are recognized to be in a ‘polymedicated’ state. This is especially true of the elderly, and of patients with concomitant cardiovascular or non-cardiovascular comorbidity. Lipid therapy in people with diabetes should ideally have low risk of drug–drug interactions. While most statins are safe, one should be aware of potential drug–drug interactions. Antifungal agents such as itraconazole, commonly prescribed in diabetes, may increase atorvastatin and simvastatin concentrations by inhibiting CYP3A4, which metabolizes these statins.

The choice of therapy for dyslipidaemia is based upon the type of lipid abnormality, not the presence or absence of various components of Metabolic Syndrome. The dosage of lipid-lowering therapy also depends upon the extent of lipid-lowering required, not upon body weight, blood pressure, or glycaemia.

Recent meta-analysis has revealed a slight risk of new-onset diabetes in persons on statin therapy. However, the benefit: risk ratio is tilted in favour of statins, and diabetes or impaired glucose tolerance is not seen as a contraindication to use of the drug class.

Statins do not affect body weight and can be used irrespectively of body mass index. Bile acid sequestrants, such as colestervam, improve glycaemia, and are approved for use as anti-diabetic drugs as well. However, this does not make them drug of first choice in diabetes and dyslipidaemia.

**Fibrates**

Fenofibrate is the most widely used fibrate compound, and is recommended as add-on to statins. Addition of fenofibrate to statin therapy may benefit patients with diabetes, hypertriglyceridaemia and low HDL-C. Gemfibrozil can also be used in patients with triglycerides >200mg% and HDL-C <40mg%, who do not respond to statin monotherapy. However, it does not offer any advantages as compared to fenofibrate. Monotherapy with fibrates is suggested only in patients with isolated hypertriglyceridaemia who do not tolerate statin therapy, even at low doses.

Fibrates are known to worsen homocysteine levels, which may underlie the increased trend of deep venous thrombosis and pulmonary embolism noticed in the FIELD study. N-3 fatty acids are known to have antithrombotic effects which may cause bleeding tendencies. This is especially important when n-3 fatty acids are co-prescribed with aspirin, a drug commonly used in diabetes.

**Statin-fenofibrate Combination**

Fenofibrate and statin combination is an effective method of managing atherogenic combined dyslipidaemia, often observed in diabetes. If possible fibrates should be prescribed in the morning and statins in the evening, to ensure staggering of peak dose concentrations. Fixed Dose Combinations of statins and fibrates provide the advantage of convenience and enhanced concordance, and can be prescribed at any time of the day.

**Other Drugs**

Colestervam is a bile acid sequestrant, is a lipid-lowering drug which has been approved for use as an oral hypoglycaemic agent as well. However, this does not make it a first line drug for use in dyslipidaemia complicated by diabetes. Cholesterol absorption inhibitors (ezetimibe) have no impact on glycaemia, and can be used in combination with statins. Niacin is not recommended for use now.

**Management of Glycaemia**

Management of glycaemia is essential in persons who have diabetes. Of the various anti-diabetic drugs, insulin has the maximum effect on triglycerides. Insulin is the drug of choice in persons with diabetes and severe hypertriglyceridaemia, as it prevents acute pancreatitis. Management of insulin resistance helps manage dyslipidaemia as well. Patients with severe hypertriglyceridaemia (>440mg%) should be admitted if symptomatic, or at risk of developing acute pancreatitis, and started on insulin therapy to achieve tight glycaemic control.

Pioglitazone has beneficial effects on lipids as well, which are explained by its structural affinity to fibrates, and its use in low dose is encouraged, provided there is no evidence of heart failure. Incretin-based therapy, including the glucagon-like peptide 1 analogues (lixisenatide, exenatide) and gliptins (vildagliptin, alogliptin, sitagliptin) also improve deranged lipid levels in people with diabetes. This is postulated to be due to reduction in lipolysis, and an improvement in the metabolism of postprandial intestinal triglyceride-rich lipoprotein particles. These drugs have multiple mechanisms of action which hold the potential to reduce CVD, including their effects on reduction of triglycerides, increase in HDL, and improvement in glucose control.
on free fatty acids or on glucose levels. The greatest effect on triglyceride levels is seen with lixisenatide.

Management of Comorbid Obesity and Nonalcoholic Steatohepatitis

Statins are safe to use in nonalcoholic steatohepatitis, with mild to moderate elevation of liver enzymes. Obese individuals with diabetes and dyslipidaemia should be treated in a manner similar to those without other features of metabolic syndrome. Atorvastatin has been shown to have relatively less benefit in obese persons in the REVERSAL study and CHIBA trial. The lipophilic nature of the drug may promote drug redistribution in the adipose tissue, thus reducing its efficacy. Pitavastatin has been reported to have better results in obese persons. This effect may be due to an increase in lipoprotein lipase expression in 3T3-L1 preadipocytes, which is otherwise suppressed in insulin resistance.

The nature of dyslipidaemia does not change the choice of anti-obesity drugs. However, severe hypertriglyceridaemia may be an indication for initiating orlistat therapy in an otherwise borderline clinical situation. Orlistat has significant beneficial effects on total cholesterol and LDL-C, which are greater than, and independent of, its effects on body weight.

Management of Comorbid Hypertension

Hypertension occurring in conjunction with dyslipidaemia is treated as per routine practice. Lipid levels do not impact the choice of antihypertensive therapy. Antihypertensive drugs such as thiazide diuretics may negatively impact lipid and other metabolic parameters. However, this effect is usually insignificant. Amlodipine can be used in hypertensive patients with dyslipidaemia. However, it should not be used in combination with high doses (>20mg/day) of simvastatin.

Monitoring

In persons who experience deterioration of diabetes control or considerable weight gain, frequent lipid estimations are estimated. Lipid profile can be checked at 6 weekly intervals till goals are achieved. People with sudden worsening of glycaemia after initiation or escalation of statin therapy may benefit from temporary cessation of the offending drug, or substitution with another statin molecule with different metabolism.

Liver enzyme should be assessed with routine diabetes monitoring, especially before and 3 months after initiation of pharmacotherapy. Creatine kinase should be measured only in patients with myalgia. Bile acid sequestrants (cholestyramine, colestipol, colesevelam) may reduce blood glucose and increase triglycerides, and careful monitoring should be done in people with diabetes.

References