ABSTRACT:

Diabetic Dyslipidemia in India is one of the main culprits for CAD in Diabetics. Non-HDL cholesterol is the main target and LDL-cholesterol particle size is an important aspect for consideration. Besides glycemic control combination of statin and fenofibrate may be more applicable. Indian diet with excess carbohydrate is another area of concern. Newer molecule for obesity, insulin resistance and atherogenic-dyslipidemia is the need of the hour.

Key words: CAD: Coronary artery disease, LDL: Low-Density Lipoproteins; TG: Triglyceride, DM: Diabetes Mellitus, CHD: Coronary Heart Disease; HDL: High-Density Lipoproteins, CRP

INTRODUCTION

Coronary artery disease (CAD), which is the most common cause of mortality in diabetic patients, is strongly associated with increased levels of serum low-density lipoproteins (LDL).

Table 1: Shows representative investigations of dyslipidemia in the Asian Indians residing in India. Overall the prevalence of dyslipidemia ranged from 10-73%. Specifically, prevalence of hypercholesterolemia was 28% in urban subjects as compared to 22% in the rural subjects.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age group (y)</th>
<th>Total cholesterol</th>
<th>Triglycerides</th>
<th>Low-density lipoprotein cholesterol</th>
<th>High-density lipoprotein cholesterol</th>
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<tr>
<td>Vikram et al, 2003</td>
<td>14-25</td>
<td>M: 3.45±0.64 (331)</td>
<td>M: 0.94±0.34 (331)</td>
<td>M: 1.8±0.61 (331)</td>
<td>M: 1.22±0.17 (331)</td>
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<tr>
<td>F: 3.87±0.65 (46)</td>
<td>F: 0.95±0.34 (46)</td>
<td>F: 2.24±0.62 (46)</td>
<td>F: 1.92±0.17 (46)</td>
<td>F: 0.93±0.26 (46)</td>
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<tr>
<td>Lubree et al, 2002</td>
<td>30-50</td>
<td>4.26±0.88 (150) §</td>
<td>1.18 (150) §</td>
<td>ND</td>
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<td>Bhattacheraya et al, 1979</td>
<td>20-60</td>
<td>M: 5.5±1.1 (184)</td>
<td>M: 0.92±0.34 (184)</td>
<td>M: 0.93±0.26 (184)</td>
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<td>F: 6.4±1.6 (77)</td>
<td>F: 0.88±0.40 (77)</td>
<td>F: 2.04±0.52 (77)</td>
<td>F: 1.72±0.45 (77)</td>
<td>F: 0.93±0.26 (77)</td>
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<td>Snehathaa et al, 2000</td>
<td>≥ 40</td>
<td>M: 5.1±1.0 (396)</td>
<td>M: 1.65±1.59 (396)</td>
<td>M: 1.22±0.17 (396)</td>
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<td>F: 5.3±1.0 (258)</td>
<td>F: 1.48±1.6 (258)</td>
<td>F: 1.72±0.52 (258)</td>
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<td>Mohan et al, 2001</td>
<td>≥ 20</td>
<td>4.92±0.13 (479) *</td>
<td>1.5±0.9 (479) *</td>
<td>ND</td>
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<td>Chadha et al, 1997</td>
<td>25-64</td>
<td>M: 5.3±1.0 (681)</td>
<td>M: 1.62±0.54 (681)</td>
<td>M: 0.93±0.26 (681)</td>
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<td>F: 4.1±0.17 (1084)</td>
<td>F: 1.57±0.57 (1084)</td>
<td>F: 1.72±0.52 (1084)</td>
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<td>Gupta et al, 1997</td>
<td>20-60+</td>
<td>4.55±1.1 (199) §</td>
<td>1.87±0.62 (199) §</td>
<td>M: 1.0±0.1 (199) §</td>
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<td>Vikram et al, 2003</td>
<td>18-65</td>
<td>M: 4.67±1.02 (170)</td>
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<td>Gupta et al, 1997</td>
<td>20-60+</td>
<td>4.27±0.95 (202) §</td>
<td>1.37±0.51 (202) §</td>
<td>2.5±0.85 (202) §</td>
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<td>F: 4.64±0.7 (100)</td>
<td>M: 1.63±0.33 (100)</td>
<td>M: 2.6±0.74 (100)</td>
<td>M: 1.3±0.29 (100)</td>
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</tr>
<tr>
<td>F: 4.64±0.7 (259)</td>
<td>F: 1.58±0.28 (259)</td>
<td>F: 2.57±0.62 (259)</td>
<td>F: 1.34±0.24 (259)</td>
<td>F: 1.34±0.24 (259)</td>
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All values in mmol/L. Numbers with parentheses indicate the number of males or females, respectively. M: males; F: females. *Total number of subjects including males and females. § Only male subjects ND: not done
Numerous studies have shown the reduction in cardiovascular morbidity and mortality with statin therapy, which can be attributed to the lowering of LDL cholesterol in addition to pleotropic effects of statins. In spite of advancement in our therapeutic armamentarium, there has not been much reduction in cardiovascular mortality in diabetic patients comparable to that in non-diabetic. Diabetic patients are known to have high levels of serum triglyceride (TG) and low levels of high-density lipoproteins (HDL). Low levels of serum HDL might be the missing link, which also has shown to have a strong correlation with cardiovascular disease. American Diabetes Association (ADA) guidelines recommend maintaining serum levels of TG below 150 mg/dl, LDL cholesterol below 100 mg/dl and HDL cholesterol of more than 40 mg/dl in males and 50 mg/dl in females. The real culprit is the dyslipidemic burden. In fact, normolipidemic dyslipidemia seen in Asian Indians may have abnormal lipid fractions. Asian Indians have abnormal lipid ratios, lower HDL values and have abnormal triglycerides and triglyceride-rich lipoproteins. The ‘low HDL’ syndrome and ‘normolipidemic’ dyslipidemia among native Indians may result from over-production or lack of clearance of the lipoprotein particles, or may be related to other defects in the apolipoproteins or metabolic enzyme deficiencies. The pathways and means of lipid metabolism in the human body reflect interactions of genetics, complex biochemical processes influenced by medical disorders, medications, and/or environmental factors.

**DYSLIPIDEMIA IN ASIAN INDIESN**

It is opined that although the total cholesterol levels in Asian Indians is similar or lower as compared to Caucasians and atherogenic dyslipidemia is more common, which may contribute to CHD. Table 1 shows representative investigations of dyslipidemia in the Asian Indians residing in India. Overall the prevalence of dyslipidemia ranged from 10-73%. Specifically, prevalence of hypercholesterolemia was 28% in urban subjects as compared to 22% in the rural subjects. (1)

In urban New Delhi, the prevalence rate of hypertriglyceridemia was 61% in non-obese subjects as compared to ~73% in obese subjects. (2) Subjects belonging to low socio-economic stratum and residing in the urban slums also showed substantial prevalence of hypercholesterolemia (~27%) and hypertriglyceridemia (~12-17%). (3, 4) However, it is difficult to compare observations of the various studies due to different sampling procedures, heterogeneity in the population samples, different methodologies used for estimations of lipoproteins and different cut-offs taken to define dyslipidemia. Figs. 1 and 2 show average levels of serum triglycerides and HDL-cholesterol from collected data from several studies in various subpopulations of Asian Indians as compared with Caucasians, respectively.

The serum triglyceride levels are highest in urban Asian Indians residing in India and migrant Asian Indians. Further, even the average serum triglyceride level of rural-based Asian Indians is higher than that in Caucasians (Fig. 1). The highest average levels of HDL-cholesterol among Asian Indians have been reported from the physically active Asian Indians residing in rural India (Fig. 2). Gupta et al. (1997) showed that ~24% of the urban population of north India had low levels of HDL-cholesterol. It is found from studies of Mishra et al., that low levels of HDL-C levels recorded in 15-16% of the people belonging to low socio-economic stratum living in New Delhi. (4) No investigator, however, has studied isolated low HDL-C levels in healthy Asian Indians residing in India. It appears that average HDL-cholesterol concentrations in all Asian subgroups whether residing in India or elsewhere are lower than Caucasians. For example, according to Tai et al. ~34% of the subjects with isolated low HDL-cholesterol levels in the multi-ethnic population in Singapore were Asian Indians. (5) They further added that a higher number of Asian Indians with low levels of HDL-cholesterol and hypertriglyceridemia had glucose intolerance, were obese, and had higher degree of insulin resistance as compared to Chinese and Malays. (5)

Population based studies on lipid profiles done in India have shown some interesting results. The triglyceride levels revealed a U shaped distribution in upper, middle and lower socio-economic
groups respectively. While higher triglyceride levels in the upper socio economic group is very likely to be due to higher fat intake compounded with slower VLDL clearance, relatively higher levels in the lower socio economic group is mostly due to very high carbohydrate diet.(6) A recent study done by Parikh et al showed that the most common pattern of dyslipidemia is high LDL and low HDL among both males and females with type 2 diabetes. The most prevalent problem among males is high LDL while among females low HDL emerged as a bigger threat.(7)

**Low Body Weight Type 2 Diabetes Mellitus (DM)** (Lean Type-2 DM)(6,8,9): The diabetic state differentiates Lean type-2 DM from protein energy malnutrition in many respects including lipid profile. Cholesterol content in LDL and VLDL are higher as is triglyceride content, although the absolute values of these lipid levels are much lower than in well nourished diabetics. Levels of mean HDL cholesterol are visibly higher in Lean type-2 DM irrespective of glycemic status. The triglyceride levels in Indian subjects with diabetes mellitus are higher both in Lean type-2 DM as well as in well nourished diabetics when compared with data from the west. This profile is likely to be the true reflection of the influence of nutritional status on lipid profile in developing societies, rather than a consequence of any specific biological alterations. A diabetic lives in his/her own socio economic group and is so bound to share similar nutritional habits.

Studies done by Seshiah et al from Chennai have also revealed similar lipid profile in obese, non-obese and lean diabetics in their population(10). While in the well nourished diabetics there was a positive correlation suggesting slower removal of triglyceride in the obese, there was no correlation in the Lean type-2 DM. Studies on Lean type-2 DM have shown that pre-existing dyslipidemia found in an uncontrolled state improves with establishment of glycemic control. Hypercholesterolemia is very unusual in such patients with diabetes.

The Indian phenotype has certain special characteristics:-

1. Hyperinsulinemia and glucose intolerance are more common among healthy Indians.
2. Indian obesity phenotype which results in increased visceral adiposity even at low BMI.
3. High level of triglyceride, low HDL cholesterol and high levels of LDL cholesterol characterize typical Indian lipid profile.
4. Higher level of pro-coagulant plasminogen activator inhibitor-1(PAI-1) has been demonstrated in Indians.
5. Higher level of soluble cell adhesion molecules, markers of endothelial dysfunction have been found even in healthy Indians.
6. Higher level of intramyocyte fat deposition have been reported.
7. Higher levels of C-reactive protein(CRP) and erythrocyte sedimentation rate(ESR) indicating intra-plaque inflammation have been reported in Indians.
8. Increased urbanization and lifestyle changes have increased levels of obesity and therefore metabolic syndrome.
9. Adverse environment during fetal life leading to low birth weight as is common in India is associated with greater incidence of insulin resistance later in life.

Diabetic dyslipidemia is also closely related to the prevalence of metabolic syndrome and both these conditions when present increases the risk of cardiovascular disorders. Considering the uniqueness of Indian population the IDF criteria for metabolic syndrome seems more logical:-

According to IDF guidelines for a person to have metabolic syndrome they must have central obesity (waist circumference: male ≥ 90cm, female ≥ 80cm for south Asian population) plus any two of the following four factors:-

1. Raised Triglycerides 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
2. Reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
3. Raised blood pressure systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
4. Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If above 5.6 mmol/L or 100 mg/dL, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome.

**Concept of Non-HDL Cholesterol**

Non-HDL cholesterol measurement provides a single index of all atherogenic, apolipoprotein (apo) B containing lipoproteins – LDL, VLDL, IDL and lipoprotein (a). Measurement of non – HDL cholesterol is more practical, reliable and inexpensive and is accepted as surrogate marker for apoB in clinical practice. Unlike LDL cholesterol which can be incorrectly calculated in presence of post-prandial hypertriglyceridemia, non HDL cholesterol is reliable when measured in the non-fasting state.

Non-HDL cholesterol which can be easily calculated as total cholesterol- HDL cholesterol is extremely important in diabetics because LDL level may not be significantly elevated in these cases. Moreover, non- HDL cholesterol is particularly atherogenic in presence of hypertriglyceridemia that usually accompanies diabetics.

There is also evidence to suggest that, in patients with diabetes, non HDL cholesterol is a stronger predictor of mortality from CHD than LDL-cholesterol. In a post-hoc analysis of four prospective
Management of diabetic dyslipidemia

Medical nutrition therapy

There is little evidence from clinical trials to determine the effect of different dietary interventions on the incidence of cardiovascular events. Observational studies suggest that patients who report healthier diets and greater physical activity have fewer cardiovascular events (11,12). The American Diabetic Association (ADA) has made recommendations for both medical nutrition therapy (MNT) and physical activity. Many patients will require a cardiac evaluation prior to beginning an exercise program. Weight loss and increased physical activity will lead to decreased triglycerides and increased HDL cholesterol levels and also to modest lowering of LDL cholesterol levels. Patients with diabetes who are overweight should be given a prescription for MNT and for increased physical activity. The proportion of saturated fat in the meal plan should be reduced. The ADA suggests an increase in either carbohydrate or monounsaturated fat to compensate for the reduction in saturated fat. Some studies suggest that a high-monounsaturated fat diet may have better metabolic effects than a high-carbohydrate diet, although other experts have suggested that such a dietary modification may make weight loss more difficult in obese patients with diabetes.

The broad guidelines are as follows-

• Total fat intake should be less than 30% of total calories.
• Saturated fat intake should be less than 10%.
• Monounsaturated fats should replace polyunsaturated fats.
• To consume at least five portion of fresh fruits and vegetables daily.
• Total cholesterol intake to be kept less than 300mg/day.
• Fish oils which contain omega three fatty acids should be consumed.

Recommendations of the American Heart Association for patients with CVD have suggested that the maximal MNT typically reduces LDL cholesterol 15–25 mg/dl (0.40–0.65 mmol/l). Lifestyle intervention may be evaluated at regular intervals, with consideration of pharmacological therapy between 3 and 6 months.

It has been noted that glucose-lowering agents sometimes lower triglyceride levels, though they usually have only a modest effect on raising HDL levels. Thiazolidinediones may raise HDL significantly, but may also increase LDL. LDL also may decrease 10% to 15% when optimal glycemic control is achieved, and LDL particles may become less atherogenic. However, complete reversal of dyslipidemia by improved control of hyperglycemia is usually unachievable.

Although the severity of dyslipidemia can be reduced by glycemic control and weight reduction, hypolipidemic drugs should be considered to reduce the risk of coronary heart disease (CHD) in diabetic patients. The four main types of drugs used for managing dyslipidemia are nicotinic acid, bile acid sequestrants, hydroxymethyl-glutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), and fibric acid derivatives (fibrates).

The ADA has made recommendations for the treatment of dyslipidemia in adults with diabetes. Treatment of elevated LDL is considered the first priority for pharmacologic therapy of dyslipidemia, based on existing research demonstrating a reduction in CHD following such treatment. The first choice for therapy is statins, and the second choice is a bile acid binding resin or fenofibrate.

The second goal for treating diabetic dyslipidemia is to increase HDL levels. For this goal, the ADA recommends initially using behavioral interventions, such as weight loss, increased physical activity, and smoking cessation. These should be followed with glycemic control and treatment with fibrates or nicotinic acid (with careful monitoring of glycemic control).

Lowering triglycerides is the third goal defined by the ADA. Glycemic control is the first priority, followed by use of a fibric acid derivative (gemfibrozil or fenofibrate). The ADA notes that statins are moderately effective at lowering triglycerides when used at high doses in hypertriglyceridemic patients who also have high levels of LDL.

For patients with combined hyperlipidemia, the ADA recommends improved glycemic control plus high-dose statin therapy as the first choice. The second choice is improved glycemic control and a statin plus a fibric acid derivative (gemfibrozil or fenofibrate). The third choice is improved glycemic control and a bile acid binding resin plus a fibric acid derivative (gemfibrozil or fenofibrate) or a statin plus nicotinic acid (with glycemic control carefully monitored).

In the management of Diabetic Dyslipidemia in Indian Scenario the justification for our LDL-centric approach should be assessed because most of our patients show higher values of triglyceride and lower HDL cholesterol levels. But, it is seen that the cholesterol levels treatment Trialist; meta-analysis of over 90,000 patients in randomized statin trials found that in people with a history of diabetes (including those without previous history of vascular disease) statins reduced the 5 year incidence of coronary events by 25% for each 39mg/dl of reduction in LDL cholesterol (P<0.001).

The other most sensitive question is which statin should be preferred in Indian scenario. In fact there is very little to choose between the three musketeers – Simvastatin, Atorvastatin and Rosuvastatin, data from the (in the simvastatin in low HDL
cholesterol Diabetes Treatment Trial of Efficacy Substudy (n=151) showed the intensive statin therapy can also improve LDL particle composition in type 2 diabetes. 40 and 80mg simvastatin lower all four LDL subclasses by 19-48% and can reduce atherogenic triglyceride rich lipoproteins (lowering VLDL by 32-40%) and LDL(53-57%).

Rosuvastatin verses Atorvastatin in Type2 diabetes Mellitus Study, 10-40mg rosuvastatin significantly reduced lipid & lipoprotein. Fractions compared. With (10-80mg) Atorvastatin on ApoB / ApoA, ratio in patients with Type2 DM and Dyslipidemia Study – it seen that results of both these statins are almost same and 90% achieve LDLC or non-HDLC target.

CONSIDERATIONS IN THE TREATMENT OF ADULTS WITH TYPE ONE DIABETES

Patients with type 1 diabetes who are in good glycemic control tend to have normal levels of lipoproteins, unless they are overweight or obese, in which case they may get a lipid profile very similar to that seen in type 2 diabetes. Their composition of lipoproteins may be abnormal, but the effects of these compositional abnormalities in relation to CVD are unknown. There is relatively little observational data on lipoproteins and CVD, and there are no clinical trials relating lipoproteins to CVD. It seems reasonable that if patients with type 1 diabetes have LDL cholesterol levels that are above the goals recommended for those with type 2 diabetes (<100 mg/dl), they should be aggressively treated. Improved glycemic control may be even more important in those with type 1 diabetes than in those with type 2 diabetes for reduction of CVD (e.g., Wisconsin Epidemiologic Study of Diabetic Retinopathy [WESDR]).

CONCLUSION:

Priorities in the management of Diabetic Dyslipidemia in Indian scenario definitely evolve around the facts of low HDLC scenario and higher triglyceride ratio. This is better to consider about both lowering of LDLc and improving the quality and size of the LDLc particle. Reaching the target LDLc level or even lowering below the recommended target level must be the main target.

Fat restriction in the diet may be the main target in west but carbohydrate restriction is also very essential in Indian diet. Excess carbohydrate generates excess fat. HDLc raising approaches like exercise, yoga and niacin should be considered in the therapeutic approach. Combination of statins & fenofibrate, may tackle mixed dyslipidemia in diabetics comprehensively. Newer molecules and approaches are necessary for comprehensively tackling mixed dyslipidemia & insulin resistance in Indian Diabetic patients.

REFERENCE: